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Investigational Antimicrobial Agents of 2013

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(continued)

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SUMMARY

New antimicrobial agents are always needed to counteract the resistant pathogens that continue to be selected by current therapeutic regimens. This review provides a survey of known antimicrobial agents that were currently in clinical development in the fall of 2012 and spring of 2013. Data were collected from published literature primarily from 2010 to 2012, meeting abstracts (2011 to 2012), government websites, and company websites when appropriate. Compared to what was reported in previous surveys, a surprising number of new agents are currently in company pipelines, particularly in phase 3 clinical development. Familiar antibacterial classes of the quinolones, tetracyclines, oxazolidinones, glycopeptides, and cephalosporins are represented by entities with enhanced antimicrobial or pharmacological properties. More importantly, compounds of novel chemical structures targeting bacterial pathways not previously exploited are under development. Some of the most promising compounds include novel β-lactamase inhibitor combinations that target many multidrug-resistant Gram-negative bacteria, a critical medical need. Although new antimicrobial agents will continue to be needed to address increasing antibiotic resistance, there are novel agents in development to tackle at least some of the more worrisome pathogens in the current nosocomial setting.

INTRODUCTION

The terms "crisis," "disaster," "preantibiotic era," and "postantibiotic era" have all been used to describe the status of antibiotic discovery and development over the past decade (1–6). Although antibiotic resistance continues to increase (6) and pharmaceutical companies continue to debate the profitability of introducing new antibacterial agents (7), an encouraging number of new molecules have recently been unveiled in an attempt to treat infections caused by multidrug-resistant (MDR) bacteria (8). Agents are currently in development for the treatment of some of the most recalcitrant skin, intra-abdominal, and respiratory infections caused by both Gram-positive and Gram-negative pathogens.

In this review we cover those antibacterial agents that have at least entered early phase 1 clinical trials, updating the status of those agents described by us in a 2011 survey or by other review articles that have listed new antibacterial agents in clinical trials (9–11). For each set of compounds, the medical significance and possible clinical placement are discussed. The mechanism of action and a summary of available microbiological and clinical data are presented for each of the compounds in that class that show the potential for making it through the development process to a new drug application (NDA). Structures for compounds that have appeared in the primary literature have been included. Data were collected from published literature primarily from 2010 through March 2013, Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), and Infectious Diseases Society of America (IDSA) meeting abstracts (2011 to 2012), government websites (e.g., the NIH-sponsored site http://www.clinicaltrials.gov, which provides current information about the clinical development status of any drug currently in U.S. clinical trials), and company websites when appropriate. Emphasis was placed on compounds that are in clinical trials, based on the sources cited above. Selected preclinical investigational compounds from groups or companies that have indicated publicly that these agents will soon be entering clinical development have been included (10; http://www.tballiance.org/).

Although many compounds in well-established classes are described (12), some novel classes with unexploited bacterial targets are also included, with the expectation that preexisting resistance mechanisms may not already be present. Figure 1 exemplifies the increased number of compounds that will be discussed in this compilation, including investigational agents with activity against

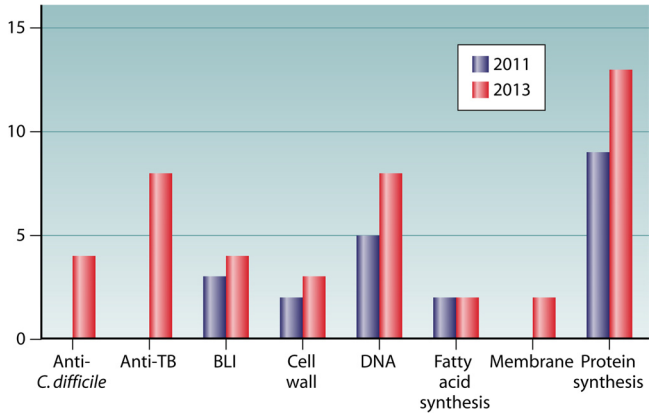

FIG 1 A comparison of investigational antimicrobial agents that have entered at least phase 1 clinical studies based on 2011 survey (9) and the current review, grouped according to bacterial target. Note that the 2011 survey did not include agents active against *Clostridium difficile* or *Mycobacterium tuberculosis*. BLI, β-lactamase inhibitors.

Mycobacterium tuberculosis and *Clostridium difficile*, agents not covered in the 2011 survey.

In efforts to encourage the development of new antimicrobial agents, several governmental actions have recently been implemented. The Food and Drug Administration (FDA)-GAIN Act, which was enacted in the United States in July 2012, provides various incentives for antibacterial research (http://finance.yahoo.com/news/gain-act-benefit-antibiotic-makers-160000929.html). One provision that applies to several of the investigational agents described in this review is the designation of a new chemical entity as a qualified infectious disease product (QIDP). Provisions of this designation include the possibility for priority review of the NDA, the potential for fast-track status for smaller population studies targeting certain resistant bacteria, and five years or longer of exclusivity following FDA approval. The European Innovative Medicines Initiative is also being used as a forum to stimulate antibacterial research and development through academic-industrial collaborations (http://www.imi.europa.eu/). As a result, some of the compounds discussed are being considered for more rapid advancement in the pipeline, helping to increase the number of agents in later stages of development. Table 1 presents a listing of the investigational antibacterial agents that will be presented in this survey, highlighting the number of new agents in clinical development. It hoped that at least some of these new drugs will eventually be approved for the treatment of drug-resistant infections.

DNA TOPOISOMERASE INHIBITORS

Quinolones

The predominant class of DNA-interacting antibacterial agents has been the quinolone antibiotics, which have proven to be valuable therapeutics for treatment of bacterial infections for over 30 years. The targets for these drugs are DNA replication enzymes: the topoisomerases DNA gyrase and topoisomerase IV. Quinolones form a ternary complex with enzyme and DNA, thus disrupting DNA replication and triggering cell death, probably due in part to oxidative damage by reactive oxygen species (13). These enzyme targets offer several important features: essentiality in bacteria, presence in all pathogens, bactericidal inhibition, differentiation from the corresponding human homolog, and the possibility of dual-target inhibition reducing the probability of mutant selection (14, 15). Quinolone drugs possess several important properties. They can have a relatively broad antimicrobial spectrum covering both Gram-positive and Gram-negative pathogens and often can be administered either orally (p.o.) or parenterally to patients. They have relatively good pharmacokinetics (PKs) and tissue distribution and are effective for multiple clinical indications, including pneumonia, septicemia, and skin and soft tissue infections. Quinolones are also distinct from many other antibacterial drugs in that they are totally synthetic rather than natural product derivatives; extensive structure-activity relationships (SAR) have been reported (16). Research on and development of new quinolone antibiotics and other topoisomerase inhibitors have continued to the present day, with several compounds in various stages of development (12, 15). Much of the recent focus has centered on improvement in Gram-positive antibacterial activity.

Nemonoxacin. Nemonoxacin (TG-875649; TaiGen Biotechnology Company) (Fig. 2, compound 1) is a novel C-8-methoxy nonfluorinated quinolone that TaiGen in-licensed from Procter & Gamble Healthcare, obtaining worldwide rights in 2011. It has completed phase 2 studies for community-acquired pneumonia (CAP) and for diabetic foot infections; recruitment is in progress for a phase 3 trial in CAP (http://www.clinicaltrials.gov). Nemonoxacin has a broad spectrum of activity against Gram-positive, Gram-negative, and atypical pathogens, including activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (MIC_{90} = 1 μg/ml) and vancomycin-resistant pathogens (17, 18). However, it was less active against Gram-negative pathogens such as *Escherichia coli*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*, with MIC_{90} values of 32, 16, and 32 μg/ml, respectively (18, 19).

In 2012, TaiGen and Zhejiang Medicine Company announced the signing of an exclusive agreement to manufacture and commercialize nemonoxacin in China, with TaiGen retaining full development and commercialization rights outside the licensed territory, including Taiwan, the United States, the European Union, and Japan (http://www.taigenbiotech.com).

Delafloxacin. Delafloxacin (RX-3341, WQ-3034, ABT-492; Rib-X Pharmaceuticals) (Fig. 2, compound 2) is an 8-chloro-fluoroquinolone that was licensed to Rib-X from Wakunaga Pharmaceutical Co. Delafloxacin contains a novel 6-amino-3,5-difluoro-

TABLE 1 Development phases of investigational antimicrobial agents with novel structures or novel targets according to company information or the FDA website http://www.clinicaltrials.gov

Phase	Antimicrobial agents
1	ACHN-975, avibactam + aztreonam, BAL30072, BC-7013, DS-8587, KPI-10, LCB01-0371, MRX-1, MUT056339, NVB302, POL7080, RPX7009 + biapenem
2	AFN-1252, AN3365, avibactam + ceftaroline, BC-3781, bedaquiline in combination, brilacidin, cadazolid, delamanid, eravacycline, fusidic acid, JNJ-Q2, LFF571, linezolid (for TB), MK-7655 + imipenem, PA-824, plazomicin, posizolid, radezolid, SQ109, sutezolid
3	Avibactam + ceftazidime, ceftolozane + tazobactam, dalbavancin, delafloxacin, finafloxacin, GSK1322322, moxifloxacin (for TB), nemonoxacin, omadacycline, oritavancin, ozenoxacin, solithromycin, surotomycin, tedizolid, zabofloxacin

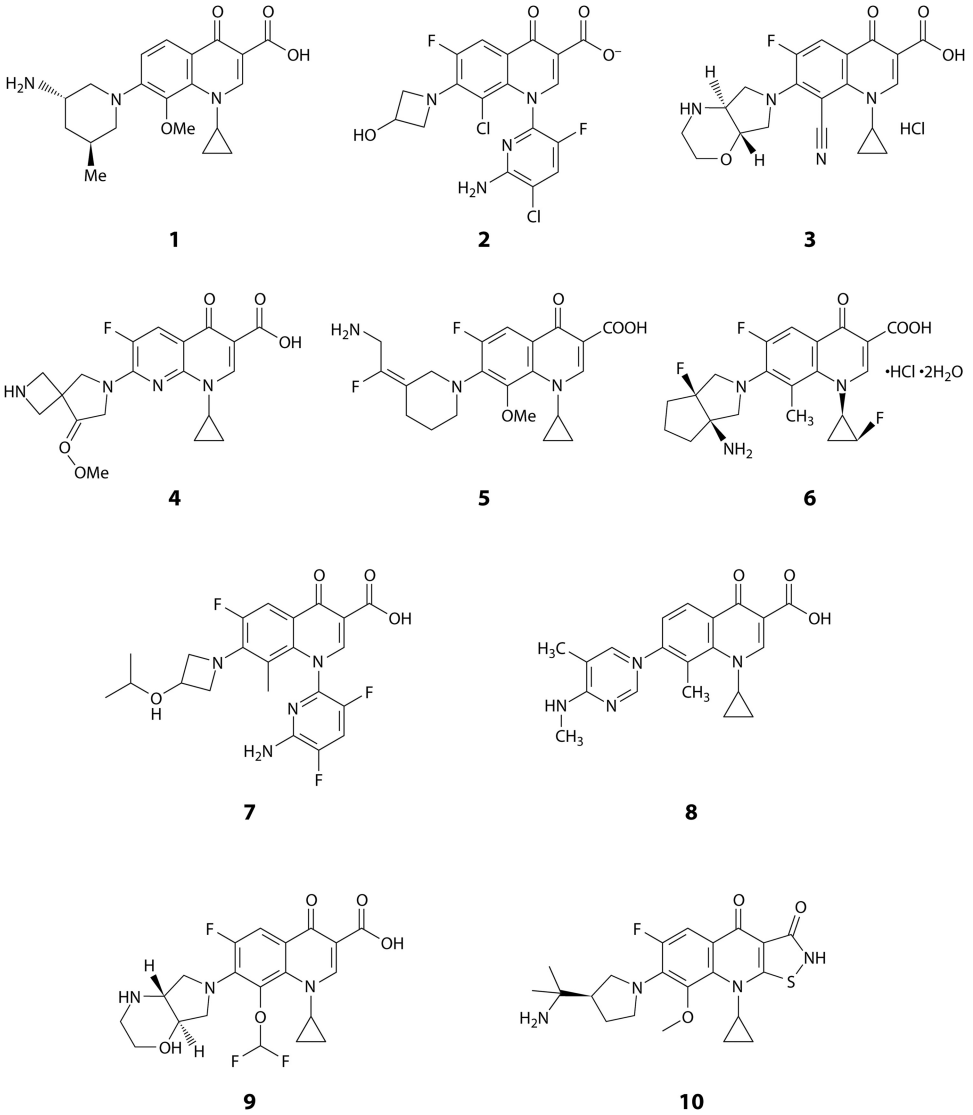

FIG 2 Structures of investigational agents that interact with DNA. 1, nemonoxacin; 2, delafloxacin; 3, finafloxacin; 4, zabofloxacin; 5, JNJ-Q2; 6, DS-8587; 7, KPI-10; 8, ozenoxacin; 9, chinfloxacin; 10, ACH-702.

pyridin-2-yl group at the N-1 position combined with a 3-hydroxyazetidin-1-yl group at the C-7 position of the quinolone core that confers improved antibacterial potency (20). It possesses potent antibacterial activity against Gram-positive bacteria, including MRSA, with MICs of 0.008 to 1 μg/ml and MIC_{50} and MIC_{90} values of 0.03 and 0.5 μg/ml, respectively (21, 22). Broad-spectrum potency was attributed to equivalence of DNA gyrase and topoisomerase IV as targets of inhibition for this compound (23). It demonstrated a low probability for the selection of resistant mutants in MRSA, and although mutants could be selected at low frequencies *in vitro* from quinolone-resistant isolates, delafloxacin MICs and mutant prevention concentrations (MPCs) were low and a fitness cost was observed (21). In phase 1 clinical studies, delafloxacin was found to be safe and well tolerated in normal healthy subjects at doses up to 900 mg; pharmacokinetic parameters increased proportionately with dose (24). Two phase 2 clinical trials for treatment of complicated skin and skin structure infections (cSSSI) have been completed (http://www.clinicaltrials.gov). Delafloxacin met primary and secondary efficacy endpoints evaluated to date and demonstrated a statistically significant efficacy advantage compared to vancomycin. Additionally, it demonstrated a numerical benefit over both linezolid and vancomycin in the secondary endpoint, cessation of lesion spread and absence or resolution of fever at 48 to 72 h, with cure rates of approximately 78%, 75%, and 73%, respectively (http://www.rib-x.com/pipeline/delafloxacin). Rib-X believes that delafloxacin demonstrated a level of efficacy that supports their planned phase 3 clinical studies.

Finafloxacin. Finafloxacin (MerLion Pharmaceuticals) (Fig. 2, compound 3) is an 8-cyano-fluoroquinolone that exhibits broad-spectrum antibacterial activity covering *Enterobacteriaceae* and Gram-positive, anaerobic, and atypical pathogens. It possesses a unique pH activation profile where antibacterial activity is enhanced in acidified environments (pH 5.0 to 6.5) common in infection sites such as urine, abscesses, wounds, chronically infected tissues, and stomach mucosa (25) (http:

//www.merlionpharma.com). MICs compared with those of other fluoroquinolones at pH 5.8 were lower by 2- to 256-fold (26). As one example, finafloxacin was superior to ciprofloxacin when tested *in vitro* against *Acinetobacter baumannii* strains under acidic conditions (27). Finafloxacin has been evaluated in phase 1 studies with oral and intravenous (i.v.) formulations and in phase 2a studies (treatment of uncomplicated urinary tract infections [UTI] and eradication of *Helicobacter pylori*) (http://www.clinicaltrials.gov). Two phase 3 trials with a topical formulation are nearing completion. MerLion signed a licensing agreement in 2011 with Alcon Pharmaceuticals to develop and commercialize the drug as an otic product for ear infections.

Zabofloxacin. Zabofloxacin (DW224a; Pacific Beach Biosciences) (Fig. 2, compound 4) is a quinolone originally developed by Dong Wha Pharmaceuticals and licensed to Pacific Beach Biosciences in 2007. It has been reported to have antibacterial activity against Gram-positive pathogens (see below), although with some loss of antibacterial activity against Gram-negative bacteria (28). Against staphylococci, the antibacterial activity of zabofloxacin was 2- to 16-fold more potent than those of moxifloxacin and ciprofloxacin. MIC_{90} values against methicillin-susceptible *S. aureus* (MSSA) and MRSA were 0.03 μg/ml and 4 μg/ml, respectively. Against *Streptococcus pneumoniae*, the activity of zabofloxacin (MIC_{90} of 0.03 μg/ml) was at least 16-fold better than those of moxifloxacin and ciprofloxacin. This strong antipneumococcal activity suggested utility for the treatment of community-acquired respiratory tract infections. Against most *Enterobacteriaceae*, antibacterial activity was 2-fold or 4-fold lower than that of ciprofloxacin but comparable to that of moxifloxacin. In regard to safety, zabofloxacin showed no adverse effects in phase 1 clinical studies, with the exception of an effect on QT interval prolongation (29). Zabofloxacin, with its expanded antipneumococcal activity, is expected to be effective for the treatment of community-acquired respiratory tract infections. It may also show utility for urinary tract infections, septicemia, systemic infections, skin and soft tissue infections, bacteremia, otitis media, and possibly endocarditis. Dong Wha is currently conducting a phase 3 clinical trial for chronic obstructive pulmonary disease with acute exacerbation (http://www.clinicaltrials.gov).

JNJ-Q2. JNJ-Q2 (JNJ-32729463; Furiex Pharmaceuticals) (Fig. 2, compound 5) is a novel fluorinated 4-quinolone originally identified and developed by Johnson & Johnson Pharmaceutical Research & Development and later licensed to Furiex. It was reported as the most potent fluoroquinolone tested, with an MIC_{50} and an MIC_{90} of 0.12 and 0.5 μg/ml, respectively, against methicillin- and fluoroquinolone-resistant staphylococcal isolates, compared to moxifloxacin, levofloxacin, and ciprofloxacin, each being at least 16-fold less active than JNJ-Q2 (30). Improved activity of JNJ-Q2 against quinolone-resistant isolates is reportedly due to its equipotent activity against DNA gyrase and topoisomerase IV as well as reduced efflux out of bacterial cells. Against *S. pneumoniae*, it had an MIC_{90} of 0.12 μg/ml, 32-fold lower than the MIC_{90} of moxifloxacin, while antibacterial activity was comparable to that of moxifloxacin against the *Enterobacteriaceae* (31). Efficacy, equivalent or superior to that of comparator quinolones, was demonstrated in murine septicemia and skin infection models with MRSA as the pathogen and in a murine lung infection model with *S. pneumoniae* (255). JNJ-Q2 possesses desirable drug-like properties, including acceptable solubility and lipophilicity. In a phase 2 clinical trial comparing efficacy, safety, and tolerability to those of linezolid, it was found to be statistically noninferior for early clinical response and well tolerated, with a favorable safety profile (32). However, primary intent-to-treat analysis was unable to declare noninferiority based on a 15% delta (a measure of comparison between arms of a controlled clinical trial that is related to a confidence interval); additional clinical data will be required for further development. Furiex is currently seeking a development partner for JNJ-Q2 (http://www.furiex.com/pipeline/discoverydevelopment-pipeline/fluoroquinolone).

DS-8587. DS-8587 (Daiichi Sankyo) (Fig. 2, compound 6) is a new fluoroquinolone with extended activity against both Gram-positive and Gram-negative pathogens, especially streptococci, staphylococci, enterococci, *E. coli*, *A. baumannii*, and anaerobes (33). The reported MIC_{90} values for *S. pneumoniae* and *S. pyogenes* were 0.03 μg/ml for both, while those for *E. coli* and *A. baumannii* were ≤1 μg/ml. Potent dual-target inhibition of both gyrase and topoisomerase IV with 50% inhibitory concentrations (IC_{50}s) of 2 μM was recently reported using *A. baumannii* enzymes (34). Also, DS-8587 was found to have a reduced propensity to select for resistant mutants and was shown to be less susceptible to efflux in this pathogen than reference fluoroquinolones. Pharmacokinetic/pharmacodynamic (PK/PD) studies in animals predicted successful treatment of hospital-associated infections as well as community-associated infections such as pneumonia with Gram-positive and/or Gram-negative pathogens, for which MICs are ≤1 μg/ml, at areas under the concentration-time curve (AUCs) in human plasma of approximately 20 to 40 μg · h/ml (35). The compound was safe and well tolerated in a number of studies in multiple animal species (36). Daiichi Sankyo lists DS-8587 as currently in phase 1 development (http://www.daiichisankyo.com/rd/pipeline).

KPI-10. KPI-10 (formerly WQ-3813, the maleic acid salt of WQ-3810; Kalidex Pharmaceuticals) (Fig. 2, compound 7) is a novel broad-spectrum fluoroquinolone containing a 6-amino-3,5-difluoropyridine at the 1 position and 3-isopropylaminoazetidine at the 7 position and with antibacterial activity against a variety of Gram-positive and Gram-negative pathogens, including drug-resistant strains such as ciprofloxacin-nonsusceptible and penicillin-nonsusceptible *Neisseria gonorrhoeae* strains (37). KPI-10 was found to be more potent than marketed quinolone comparators against key Gram-negative pathogens, particularly *E. coli* and *Klebsiella pneumoniae*, with an MIC_{90} of 2 μg/ml against more than 600 *Enterobacteriaceae* isolates (38). This was three or more doubling dilutions lower than the MIC_{90} values of levofloxacin, ciprofloxacin, moxifloxacin, or gatifloxacin (MIC_{90} range, 16 to >16 μg/ml). Against Gram-positive pathogens, it was superior in antibacterial activity to these same comparator quinolones against MSSA, MRSA, and *Enterococcus faecalis*, including quinolone-resistant isolates (39). KPI-10 completed an initial phase 1 study, which showed that in healthy volunteers single ascending oral doses were generally safe and well tolerated and that the pharmacokinetic profile may support once-daily oral dosing (40).

Ozenoxacin. Ozenoxacin (Ferrer Internacional S.A.) (Fig. 2, compound 8) is a novel nonfluorinated quinolone antibacterial agent with potent antibacterial activity against quinolone-resistant isolates that is attributed to dual inhibition of DNA gyrase and topoisomerase IV. MIC_{90} values were ≤0.25 μg/ml for quinolone-resistant MRSA isolates (41). *In vitro* and *in vivo* antibacterial activity has been demonstrated against a broad range of bacteria, including strains with resistance to quinolones. A successful

absorption, tolerability, and safety study has been completed with this topical agent in patients with impetigo (2 months to 65 years old), and clinical efficacy was demonstrated in a phase 2 dose-finding study in adult patients with secondarily infected traumatic lesions (http://www.ferrergrupo.com). Topical ozenoxacin was found to be safe and well tolerated, with no dermal absorption and no adverse effects typically associated with topically formulated halogenated quinolones. Ferrer, a privately held Spanish pharmaceutical company, has initiated a phase 3 clinical trial of ozenoxacin formulated as a 1% cream twice daily for 5 days as a topical treatment for infectious dermatological conditions (http://www.clinicaltrials.gov).

Chinfloxacin. Chinfloxacin (Fig. 2, compound 9), a quinolone under recent investigation in China, has a structure similar to that of moxifloxacin except for difluoride substitution in the 8-methoxy group. It displayed activity comparable to that of moxifloxacin, 2- to 16-fold-higher activity than ciprofloxacin and levofloxacin against Gram-positive isolates, and similar to or 2- to 8-fold-lower activity than ciprofloxacin and levofloxacin against the *Enterobacteriaceae* (42). In a mouse systemic infection model, chinfloxacin demonstrated *in vivo* activity against MSSA (with a 50% effective dose [ED_{50}] of 2.28 to 4.15 mg/kg), MRSA (ED_{50}, 14.75 mg/kg), penicillin-intermediate-resistant *S. pneumoniae* (ED_{50}, 6.20 mg/kg), penicillin-resistant *S. pneumoniae* (ED_{50}, 3.51 to 5.03 mg/kg), vancomycin-susceptible enterococci (ED_{50}, 25.02 mg/kg), vancomycin-resistant enterococci (VRE) (ED_{50}, 5.18 to 15.39 mg/kg), *E. coli* (ED_{50}, 1.25 to 1.90 mg/kg), and *K. pneumoniae* (ED_{50}, 2.92 to 8.28 mg/kg) (43). It was also found that the IC_{50} of chinfloxacin for inhibition of the hERG K^+ channel was 2-fold higher than that of moxifloxacin, suggesting the potential for lower cardiac toxicity. The current development status is unknown.

GSK2140944. GlaxoSmithKline (GSK) lists a topoisomerase inhibitor, GSK2140944 (structure unavailable), in two phase 1 clinical studies to investigate the safety, tolerability, and pharmacokinetic profile following repeat oral doses and single and repeat i.v. doses (http://www.clinicaltrials.gov).

ACH-702. ACH-702 (Achillion Pharmaceuticals) (Fig. 2, compound 10) is an isothiazoloquinolone that has structural similarities to quinolones but differs due to the presence of an isothiazolone ring (44, 45). Biochemical analyses indicated potent dual inhibition of the two antibacterial target enzymes, DNA gyrase and topoisomerase IV, with IC_{50}s of $\leq$1 μM for staphylococcal enzymes (46). The isothiazoloquinolones possess broad-spectrum antibacterial activity against important human clinical isolates, including fluoroquinolone-resistant strains, especially the Gram-positive staphylococci, *S. pneumoniae*, and enterococci. Against recent MRSA clinical isolates, ACH-702 exhibited an MIC_{90} of 0.25 μg/ml, including for quinolone-resistant isolates (46). Reduced antibacterial activity was reported for Gram-negative bacteria, with the exception of the respiratory Gram-negative pathogens. *In vivo* efficacy was demonstrated against *S. aureus* in murine sepsis and thigh infection models, with decreases in CFU/thigh equal to or greater than those observed for the vancomycin comparator (46). Rapid metabolism of the parent compound via extensive glucuronidation precluded systemic administration, and ACH-702 was recently licensed to Ora Inc. for use in ophthalmic infections (M. Pucci, unpublished data; www.achillion.com).

PROTEIN SYNTHESIS INHIBITORS

Protein synthesis inhibitors are a mainstay of antimicrobial therapy for both community-acquired and nosocomial infections. Although some of these agents are targeted for the treatment of infections caused primarily by Gram-positive pathogens, broad-spectrum agents with activity against multidrug-resistant (MDR) Gram-negative pathogens have also been identified. Because a review article by Sutcliffe in 2011 provided detailed descriptions of many investigational protein synthesis inhibitors (10), limited background material prior to 2011 is discussed below.

Aminoglycosides

Aminoglycosides were among the first antibiotics in the antibacterial armamentarium (47) and include many semisynthetic derivatives that have been widely used therapeutically because of their broad-spectrum activity against both Gram-positive and Gram-negative bacteria. Aminoglycosides inhibit bacterial protein synthesis by binding to the 16S rRNA subunit of the 30S ribosome (48). Unlike many protein synthesis inhibitors, they act as bactericidal agents, thus providing a possible advantage in terms of their use in serious infections where rapid elimination of the causative bacteria can be critical. In spite of a broad set of indications and the ability to treat infections caused by Gram-negative bacteria, aminoglycosides have fallen out of favor due to resistance development and safety concerns such as the development of reversible nephrotoxicity or of ototoxicity that is generally irreversible (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). Pharmacodynamic studies suggest that the side effect profile of older aminoglycosides could be improved by using a once-a-day dosing regimen rather than the 8-h dosing frequency that was originally approved (49).

Resistance to the aminoglycosides includes mechanisms related to endogenous chromosomal mutations affecting bacterial efflux pumps or the ribosomal binding site. More importantly, plasmid-encoded resistance determinants that have become commonly found in many MDR Gram-negative pathogens include genes encoding ribosomal methyltransferases or aminoglycoside-inactivating enzymes. These resistance factors are frequently transferred together with genes encoding multiple β-lactamases, thereby resulting in resistance to both classes of antibiotics simultaneously.

Plazomicin. Industry efforts to develop an improved aminoglycoside with an acceptable safety profile and increased resilience with respect to current resistant isolates have resulted in the discovery of the bactericidal plazomicin (ACHN-490) (Fig. 3, compound 1) by Achaogen scientists (50). Plazomicin, a semisynthetic derivative of sisomycin, had MIC_{90} values of $<$2 μg/ml against *E. coli*, serine carbapenemase-producing *K. pneumoniae*, MDR *Enterobacteriaceae* with metallo-β-lactamases, *S. aureus* (including MRSA), and *Acinetobacter* spp. that bore a variety of aminoglycoside resistance determinants (50–54). All known transferable aminoglycoside-modifying enzymes were unable to inactive plazomicin, although plasmid-carried *armA* and *rmtC* encoding ribosomal methyltransferases, such as those found in NDM-1 metallo-β-lactamase (MBL)-producing pathogens, conferred resistance to plazomicin with MICs ranging from 64 to $>$256 μg/ml (53). Plazomicin had modest activity against *P. aeruginosa*, with MIC_{50} values of 8 μg/ml, but was more potent than other aminoglycosides against *A. baumannii* (55).

Plazomicin has also demonstrated efficacy in a number of *in*

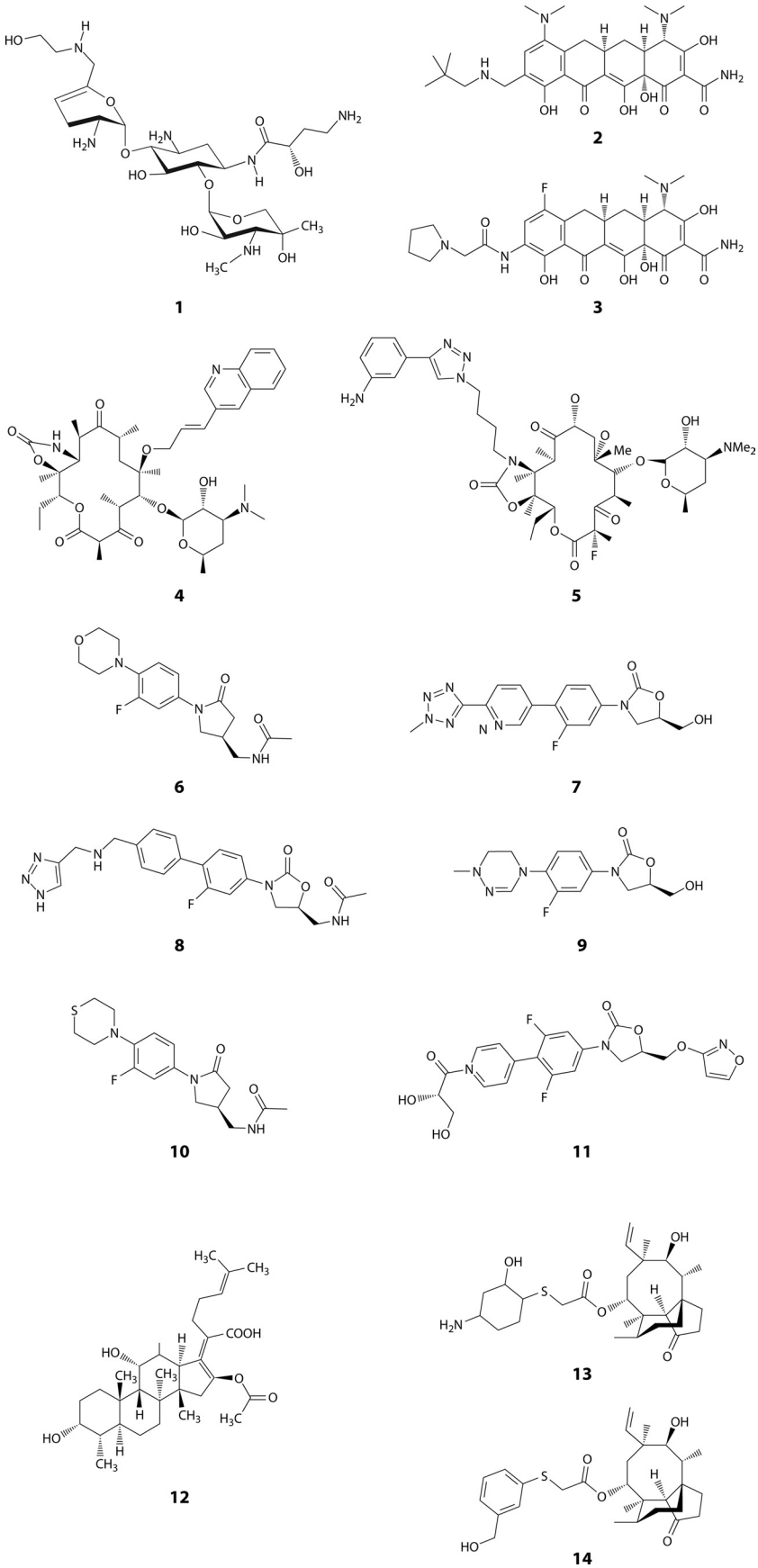

FIG 3 Structures of investigational protein synthesis inhibitors. 1, plazomicin; 2, omadacycline; 3, eravacycline (TP-434); 4, cethromycin; 5, solithromycin; 6, linezolid; 7, tedizolid; 8, radezolid; 9, LCB01-0371; 10, posizolid; 11, sutezolid; 12, fusidic acid; 13, BC-3781; 14, BC-7013.

vivo models of infection, including murine septicemia models (56) and models of inhalational plague in mice (57) and the African green monkey (58). In the neutropenic mouse thigh model, plazomicin exhibited dose-dependent activity (56) with AUC/MIC defined as the pharmacodynamically linked driver for efficacy in that model (59).

Plazomicin (i.v. dosing) has completed four phase 1 clinical trials in healthy volunteers, including the standard single- and multiple-ascending-dose studies at doses ranging from 1 to 15 mg/kg for a duration of 5 to 10 days (60), lung penetration studies, and the drug effect on the QT/QTc interval (http://www.clinicaltrials.gov). The design and outcome of the studies are outlined in detail by Sutcliffe (10). Linear, dose-proportional pharmacokinetics were observed, with no drug accumulation. A double-blind, randomized, comparative phase 2 clinical trial examining the safety and efficacy of plazomicin and levofloxacin for the treatment of complicated urinary tract infections (cUTI) and acute pyelonephritis was completed in early 2012 (http://www.clinicaltrials.gov). Coprimary endpoints of microbiological eradication at test of cure in patients who had one or two causative pathogens isolated from urinary specimens at the baseline (modified intention-to-treat [MITT] population) and in microbiologically evaluable subjects (ME population) were not statistically different for the two drugs (61).

The numbers of adverse events (AEs) were relatively low in both the phase 1 and phase 2 studies. No serious AEs were reported in the ascending-dose studies, although two reversible cases of tinnitus were reported (60). In the UTI study, mild to moderate treatment-related adverse events were reported in 17.7% of plazomicin-treated and 27.3% of levofloxacin-treated patients. No serious treatment-related AEs occurred (61). Although plazomicin has potential as a safe and effective aminoglycoside that circumvents many resistance mechanisms in MDR Gram-negative pathogens, Achaogen is continuing its search for its next-generation aminoglycoside with enhanced clinical properties (http://www.achaogen.com/pipeline/next-generation-aminoglycosides).

Tetracyclines

Tetracyclines have been used as both oral and systemic antibacterial agents for over 60 years following their discovery from soil samples in various locations in the midwestern United States (62). They act as protein synthesis inhibitors by binding to the 30S ribosomes of a wide range of both Gram-positive and Gram-negative bacteria. Because they are frequently encountered in environmental samples, class resistance has been easily selected. The most common resistance mechanisms have arisen through expression of tetracycline-specific efflux pumps, either chromosomally or plasmid encoded, or by ribosomal modifications that prevent tetracycline binding. As a result, clinical use of tetracyclines has diminished considerably. Scientists at Lederle Laboratories in the early 1990s identified a novel set of 9-glycylamido-substituted tetracyclines that they named "glycylcyclines" (63), tetracycline derivatives that were able to evade most bacterial efflux pumps and that were not affected by the TetM ribosomal protection mechanism (64). The clinical candidate tigecycline emerged from that program as an i.v. broad-spectrum antibacterial agent and was approved by the FDA in 2005 (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). Several other groups have utilized the tetracycline scaffold to design novel tetracyclines with more favorable properties, including attempts to provide both oral and systemic formulations with an improved safety profile.

Omadacycline. During a search for a broad-spectrum tetracycline that avoided resistance, Paratek scientists identified omadacycline (PTK0796; Paratek) (Fig. 3, compound 2), an aminomethylcycline with bacteriostatic activity against organisms including MRSA, MDR *S. pneumoniae*, and many MDR enteric bacteria (65, 66). The mechanism of action is protein synthesis inhibition; IC_{50}s were 2.8 μM for omadacycline and 0.9 μM for tigecycline in an *in vitro* transcription/translation inhibition assay (67). Omadacycline had greater potency against Gram-positive bacteria (MIC_{90} values of <0.5 μg/ml) than against the enteric bacteria, where MIC_{90} values ranged from 2 to 64 μg/ml against *E. coli* and *Morganella morganii*, respectively (10). Like tigecycline, omadacycline evades both ribosomal protection and common tetracycline-specific efflux mechanisms (68). However, intrinsic resistance in *P. aeruginosa* and reduced susceptibility in *K. pneumoniae* were related to (over)expression of the MexXY and AcrAB efflux pumps (69). In a murine pneumonia model, drug concentrations in lung tissue were two to four times higher than those in serum, with no evidence for binding to lung surfactant (10). Thus, omadacycline may be considered for use in the treatment of pneumonia.

Phase 1 data for i.v. dosing of omadacycline have been previously summarized (10). In contrast to the case for tigecycline, both oral and i.v. formulations are being developed. Although omadacycline was generally well tolerated, 22% of the volunteers experienced cannula site reactions after i.v. infusion, and 25% of the subjects reported mild nausea after oral administration. Orally administered omadacycline was not metabolized and was excreted primarily in the feces (81.1%) in normal volunteers (70). In a randomized, investigator-blinded phase 2 clinical trial in adults with cSSSI, step-down therapy of 100 mg of omadacycline followed by 200 mg oral therapy dosed once a day (QD) was compared to a comparable step-down regimen of linezolid (600 mg i.v./600 mg oral) dosed twice a day (BID). Success rates in the clinically evaluable and microbiologically evaluable (ME) sets were similar for both drugs (clinically evaluable success of 98% and 93.2% for omadacycline and linezolid, respectively, and ME success of 97.4% and 93.7%, respectively) (71).

Two omadacycline phase 3 studies were initiated in patients with cSSSI, with linezolid as a comparator, and moxifloxacin added for patients with infections caused by Gram-negative pathogens. By 2012, the first study had been terminated after 143 patients had enrolled; the second study was withdrawn prior to enrollment (http://www.clinicaltrials.gov) due to changes in FDA guidance (10). Newly designed double-blind, randomized, and controlled phase 3 studies using early response endpoints will now be conducted under two special protocol assessment (SPA) agreements approved by the FDA for acute bacterial skin and skin structure infections (ABSSSI) and CABP (community-acquired bacterial pneumonia) (http://paratekpharm.com/). The company is also planning additional studies for the treatment of UTI (http://paratekpharm.com/). In January 2013, Paratek announced that the FDA had designated omadacycline a QIDP for both i.v. and oral formulations in the treatment of ABSSSI and CABP (http://paratekpharm.com/).

Eravacycline. Eravacycline (TP-434; Tetraphase) (Fig. 3, compound 3) is a C-7,C-9-disubstituted fluorocycline with broad-spectrum antibacterial activity. Like the other newer tetracycline

derivatives, it demonstrated ribosomal binding and was not affected by major tetracycline-specific efflux or ribosomal protection resistance mechanisms (256). Eravacycline had MIC values of <2 μg/ml against many MDR Gram-negative pathogens, including β-lactam-resistant *E. coli*, *K. pneumoniae*, and *Acinetobacter* spp. (10). High potency was especially observed against all streptococci and enterococci, with MIC values of <0.12 μg/ml and MIC_{90} values of 0.12 and 0.25 μg/ml for MSSA and MRSA. Biofilms of uropathogenic *E. coli* were shown to be susceptible to the action of eravacycline (72). *In vivo* activity in multiple infection models corroborated the *in vitro* spectrum (10).

Eravacycline has completed phase 1 trials for i.v. dosing. A single-ascending-dose study of the oral formulation demonstrated an average of 28% bioavailability (10). In mid-2012, a phase 2 randomized, double-blind, double-dummy, multicenter, prospective clinical trial of i.v. eravacycline was completed for the treatment of adult community-acquired complicated intra-abdominal infections (cIAI) (http://www.clinicaltrials.gov). Two dosing regimens of eravacycline were compared to 1 g ertapenem dosed once a day. Clinical outcomes in the ME population at test of cure were similar for all three arms of the trial: 1.5 g of eravacycline dosed QD, 92.9%;1.0 g of eravacycline dosed at 12-h intervals, 100%; and ertapenem, 92.3%. No drug-related serious adverse events were reported, with only relatively low rates of gastrointestinal side effects of 1.9% and 10.7% for the QD and BID eravacycline formulations, respectively, compared to 6.7% for ertapenem (73). The company expects to develop an oral formulation also.

Tetraphase has several other novel tetracyclines in preclinical development, including the isoindoline pentacycline TP-834 to treat infections caused by respiratory pathogens (including MRSA) and TP-271, a novel synthetic fluorocycline with activity against respiratory pathogens, including bacterial bioterrorism agents and other MDR pathogens (http://tphase.com/pipeline/overview/). TP-834 is expected to enter phase 1 trials in the near future (http://tphase.com/pipeline/overview/). TP-271 was reported to have MIC_{90} values of <1 μg/ml against sensitive and resistant Gram-positive bacteria (including MRSA and *Enterococcus faecium*), respiratory Gram-negative pathogens, and *Acinetobacter* spp. (74). The *in vitro* profiles of these agents against problematic bacteria make them worth watching for future developments.

Ketolides

Macrolides have been used therapeutically for half a century to treat community-acquired respiratory infections. Their mechanism of action involves inhibition of bacterial protein synthesis by binding to 23S rRNA of the 50S ribosomal subunit (75). They have antimicrobial activity not only against key respiratory pathogens such as the streptococci but also against atypical bacteria, including *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* (76). Erythromycin, clarithromycin, and azithromycin have played major roles as oral antibiotics in community infections, but resistance among the pneumococci has made their efficacy less reliable, leading to the development of the ketolides, erythromycin derivatives with a C-3 ketone modification (77). Telithromycin, the first ketolide approved for clinical use, had an *in vitro* spectrum similar to that of a typical macrolide but with enhanced activity against macrolide-resistant pneumococci bearing the genes encoding the Erm(B) methylase or the MefA efflux pump (78). However, telithromycin encountered questions about adverse events and efficacy in a shifting regulatory environment, and its use has been severely limited by postapproval decisions by the FDA (79). Two additional ketolides, cethromycin and solithromycin, have reached late-stage development.

Cethromycin. Cethromycin (ABT-773; Advanced Life Sciences) (Fig. 3, compound 4) is a ketolide originally identified by Abbott scientists and later developed under the auspices of Advanced Life Sciences Inc. through phase 3 clinical trials and submission of an NDA. Cethromycin has the same mechanism of action and antibacterial spectrum as telithromycin (80) but has improved pharmacokinetic properties and greater potency against erythromycin-resistant pneumococci harboring the MefA efflux pump or the Erm(B) methyltransferase (10). In addition to its antistreptococcal activity, it has MIC_{90} values of ≤0.06 μg/ml against *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*, atypical organisms that are desirable to include in the antimicrobial spectrum of agents used to treat respiratory infections (10). During its 53 clinical studies, cethromycin demonstrated an acceptable safety profile with no evidence of hepatotoxicity (81). It has been granted orphan drug status for tularemia, plague, and anthrax prophylaxis but has not been granted FDA approval for these indications or for treatment of mild to moderate CABP (82). After the FDA issued a complete response letter for the CAPB indication requesting additional efficacy data for patients with more severe pneumonia (http://www.drugs.com/nda/restanza_090806.htmL), Advanced Life Sciences suspended operations (http://www.advancedlifesciences.com/). Considering that the patent for cethromycin expires in 2016 (10), it is unlikely that the compound will be developed further in the United States or Europe.

Solithromycin. Solithromycin (CEM-101; Cempra) (Fig. 3, compound 5) is a novel fluoroketolide that binds to the 50S ribosomal subunit with an affinity similar to that of telithromycin (83). The antimicrobial activity of solithromycin is directed against respiratory pathogens, with 99.9% of its MICs being ≤0.5 μg/ml against the streptococci and with MIC_{90} values of 2 μg/ml and 0.12 μg/ml against *Haemophilus influenzae* and *Moraxella catarrhalis*, respectively (84). *In vitro* microbiological activity against the enterococci and staphylococci was within 2-fold of that for telithromycin (85). In studies defining the interactions of various macrolides with nicotinic acetylcholine receptors at the neuromuscular junction, the optical ciliary ganglion, and the vagus nerve innervating the liver, solithromycin exhibited up to 30-fold-higher IC_{50}s than telithromycin, suggesting that the vision disturbances and liver damage associated with telithromycin use may be diminished by solithromycin (86). Cempra Pharmaceuticals conducted three phase 1 single- and multiple-dose trials in which solithromycin was deemed to be safe at single doses of as high as 1,600 mg; modest accumulation of the drug was noted at the end of a seven-day dosing period when healthy subjects received once-daily doses of 200 to 600 mg (87). The drug has completed a phase 2 CABP trial in which oral solithromycin was deemed to be safe and with efficacy similar to that of levofloxacin (http://www.cempra.com/products/Solithromycin-cem-101/). It has recently entered a phase 3 trial to assess safety efficacy in CABP (http://www.clinicaltrials.gov).

Oxazolidinones

The introduction of the oxazolidinone class of antibiotics has proven to be a valuable addition to our antibacterial drug arsenal. These novel, totally synthetic compounds were first described in 1978, with initial pharmaceutical drug development efforts in the 1980s at E. I. du Pont de Nemours & Co (DuPont) (88, 89). Two comprehensive reviews of the oxazolidinones covering the history of their discovery and development have been recently published (88, 90). The first lead compounds emerged from screening efforts designed to identify novel agents for treating selected plant diseases of fungal and bacterial origin and were initially attractive for several reasons. Their antibacterial activity displayed broad coverage of MDR Gram-positive pathogens. They were found to possess a unique mechanism of action through inhibition of protein synthesis by binding to the P site on the 23S rRNA of the 50S subunit of the bacterial ribosome. This binding prevents formation of a functional 70S initiation complex, an essential component of the bacterial translation process. Of particular interest was the finding that there was no cross-resistance to other protein synthesis inhibitors. *In vitro* generation of resistant mutants was extremely difficult using traditional laboratory methodologies. Finally, the potential availability of both oral and i.v. administration routes was supported by favorable pharmacokinetic profiles that translated into p.o./i.v. efficacy when tested in relevant animal infection models (91). These observations supported further development of oxazolidinones as a potential new class of antibacterial agents.

Extensive chemical analog work established early SAR for oxazolidinones and helped drive further optimization efforts (92–94). DuPont advanced two developmental candidates into early clinical trials but terminated these trials early due to toxicity issues (91, 95). Further work on the class was carried out at Upjohn and later at Pharmacia & Upjohn and Pfizer. Linezolid (U-100766, PNU-100766) (Fig. 3, compound 6), discovered by Upjohn scientists, then entered human clinical trials in 1995 (88, 96). Linezolid displayed acceptable safety and efficacy, was granted fast-track status because of its novel structure (92), and was approved by the FDA in 2000; it is now marketed by Pfizer after acquisition of Pharmacia & Upjohn. Although not completely eliminated, adverse events were sufficiently diminished for clinical usage (97), and it is currently the leading branded antibiotic for serious Gram-positive infections, with reported worldwide sales of $1.3 billion in 2011 (http://online.barrons.com/article/PR-CO-20120131-905496.htmL). The first clinical resistance to linezolid was due to mutational events at multiple 23S rRNA sites involving the peptidyl transferase center of the ribosome (97). Recently, linezolid resistance has been discovered in clinical isolates, mediated by the presence of the *cfr* gene product, Cfr methyltransferase, which modifies adenosine at position 2503 in 23S rRNA within the drug binding site in the large ribosomal subunit (98). Because opportunities remain to expand the spectrum, overcome resistance, and improve safety, efforts to investigate new oxazolidinone analogs have continued at several pharmaceutical companies over the past several years.

Tedizolid. Tedizolid (torezolid, TR-701, DA-7218; Trius Therapeutics) (Fig. 3, compound 7), an i.v. and orally administered second-generation oxazolidinone originating from Dong-A for the treatment of serious Gram-positive infections, including MRSA, has completed enrollment in a phase 3 clinical trial for ABSSSI. As a second-generation oxazolidinone, tedizolid was designed for improved potency, decreased resistance, and a broader spectrum of activity over the first generation of clinically developed oxazolidinones (257). Tedizolid retained activity (MIC_{90} of 0.5 μg/ml) against most linezolid-resistant staphylococci tested, including isolates with elevated linezolid MICs of >32 μg/ml. It has successfully completed phase 2 and phase 3 trials in patients with cSSSI as well as seven phase 1 trials. In addition to its more potent antistaphylococcal activity, tedizolid has been reported to offer other advantages over linezolid, including the potential for shorter dosing regimens in the treatment of ABSSSI (6 days versus 10 to 14 days) and *in vivo* bactericidal activity. It has been reported to possess more predictable drug exposure and an improved safety profile in regard to lower gastrointestinal side effects and less platelet toxicity. Trius plans to develop tedizolid phosphate, the orally active prodrug of tedizolid, to treat multiple clinical indications, including ABSSSI and other serious indications involving infections of the lung and blood, such as CABP, hospital-acquired pneumonia, ventilator-acquired pneumonia, and bacteremia. The FDA has designated tedizolid phosphate a QIDP for its current phase 3 program of tedizolid for ABSSSI as well as the planned phase 3 program for hospital-acquired/ventilator-associated bacterial pneumonia. In addition, the designations were granted for both the i.v. and oral dosage forms of tedizolid (http://investor.triusrx.com/releases.cfm).

There may be a distinct advantage for tedizolid in regard to one specific drug toxicity. Clinical observations after linezolid treatment were consistent with mitochondrial disorders caused by drugs or hereditary defects in respiratory chain complexes (99). Linezolid was found to affect human mitochondria after long-term use (100), although fortunately the effects were reversible after stopping treatment. In contrast, the potential of tedizolid to damage mitochondria was examined, and no evidence of interactions with eukaryotic mitochondria was found (101). If this cleaner safety profile is further verified, particularly after longer treatment regimens, this could translate to greater success in the marketplace, as tedizolid would represent an oxazolidinone with efficacy equal to or better than that of linezolid but with an improved safety profile.

Radezolid. Radezolid (Rx-01_667, RX-1741; Rib-X Pharmaceuticals) (Fig. 3, compound 8) is a novel oxazolidinone with a broader spectrum of coverage and increased antibacterial activity against Gram-positive bacteria compared to those of linezolid (102). It offers the potential for improved antibacterial activity in that it is 2-fold more active *in vitro* than linezolid against staphylococci and 4- to 16-fold more potent against the streptococci and enterococci. Uniquely for the oxazolidinones, radezolid also offers coverage of fastidious Gram-negative bacteria. It displayed MIC_{90} values against *cfr*-containing linezolid-resistant *S. aureus* isolates that were 4- to 8-fold lower than those of linezolid (103). Another attractive property of this compound is higher intrinsic activity than linezolid in infected cells, with phagocytic cell internal concentrations increased 11-fold over extracellular concentrations (104, 105). The compound has recently successfully completed two phase 2 clinical trials for community-acquired pneumonia (CAP) and for uncomplicated skin and skin structure infections (uSSSI) (http://www.clinicaltrials.gov). In October 2012, the FDA designated radezolid a QIDP for the indications of ABSSSI and CABP (http://www.rib-x.com/investors/press-release_2012_10_10.php).

MRX-1. MRX-1 (MicuRx Pharmaceuticals; http://www.micurx

.com) (structure unavailable) is a next-generation oral oxazolidinone antibiotic for treating Gram-positive bacterial infections, including MRSA and VRE isolates, with an MIC_{90} for MRSA of 0.5 μg/ml, which was half of that required for linezolid (106). In preclinical studies, MRX-1 was shown to effectively cure *in vivo* systemic and localized thigh infections in mice due to Gram-positive bacteria, including MRSA and VRE (107). Preclinical toxicology studies demonstrated safety, with a low tendency to induce myelosuppression compared with other oxazolidinones, including linezolid. In a 4-week, repeat-dose preclinical study in rats comparing MRX-1 to linezolid, MRX-1 exhibited exposure levels similar to those of linezolid, but with no adverse effects observed at a dose level of 100 mg/kg. A phase 1 study explored safety, tolerability, and pharmacokinetics of MRX-1, both in single ascending doses up to 1,800 mg and in 15-day multiple-dose regimens of twice-daily 600 mg and 800 mg (108, 109). The compound was found to be safe and well tolerated at all doses, with no evidence of myelosuppression at exposure levels similar to those for linezolid.

LCB01-0371. LCB01-0371 (LegoChem Biosciences) (Fig. 3, compound 9) is a novel oxazolidinone containing a cyclic amidrazone. Antibacterial activity was found to be comparable to that of linezolid, with MIC_{90} values of 2 μg/ml against MRSA and MSSA isolates (110). *In vivo* efficacy of orally administered LCB01-0371 against systemic infections in mice was 2- to 4-fold greater than that of linezolid in treating infections caused by both *H. influenzae* and Gram-positive pathogens. This compound had high aqueous solubility and good absorption, distribution, metabolism, excretion, toxicity, and pharmacokinetic profiles. LCB01-0371 has completed a phase 1 clinical trial of safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy male subjects run as a randomized, double-blind, placebo-controlled, single-dose, dose escalation study and is now being studied in a multiple-ascending-dose study in healthy volunteers (http://www.clinicaltrials.gov).

Posizolid. Posizolid (AZD5847, AZD2563; AstraZeneca) (Fig. 3, compound 10) has been reported to possess potent antibacterial activity against a variety of Gram-positive bacteria regardless of resistance to other classes of antibiotics. MICs for staphylococci, pneumococci, and enterococci ranged from 0.25 to 2 μg/ml, with modal MICs of 1 μg/ml for staphylococci and pneumococci and 1 to 2 μg/ml for enterococci (111). The MICs of posizolid were found to be either the same as those of linezolid or 2-fold lower. This compound is under development by AstraZeneca for the treatment of tuberculosis (TB) and is further discussed below. Another oxazolidinone, sutizolid (PNU-40080; Pfizer) (Fig. 3, compound 11), is also under development for tuberculosis treatment and will also be discussed further below.

Fusidic Acid

The fusidane natural product fusidic acid (CEM-102; Cempra) (Fig. 3, compound 12) is a surprising investigational drug in this review because it is commonly utilized throughout the world, except for the United States. It has been safely used in Europe since the early 1960s as a treatment for staphylococcal infections and is now prescribed as oral therapy to treat patients with community-associated MRSA infections (112). Fusidic acid is active primarily against Gram-positive bacteria, especially staphylococci, and inhibits protein synthesis by locking elongation factor G (EF-G) to the ribosome after GTP hydrolysis (258).

Cempra Pharmaceuticals has undertaken the development of an oral formulation of the drug as CEM-102 to treat community infections caused by MRSA in the United States. Promising phase 2 clinical data in ABSSSI, using a loading-dose regimen that may suppress resistance, demonstrated that the CEM-102 safety, tolerability and efficacy were not statistically significant from those of the comparator, linezolid (259). Resistance development has become a critical issue for fusidic acid in some parts of the world. Countries that have used fusidic acid for some time have varied resistance problems. Resistance rates ranged from 1.4% for *S. aureus* in Sweden (260) to 89% in community-acquired MRSA in Greece (116); in Canada, where fusidic acid is also approved, resistance in *S. aureus* was 7.0% in the 2007-2008 time period, during which time only 0.3% of *S. aureus* isolates in the United States were fusidic acid resistant (117). Because of concerns about resistance, it has been suggested that fusidic acid should be dosed in combination with another orally active anti-MRSA drug such as rifampin. Cempra is currently conducting a phase 2 clinical trial in which the oral combination of CEM-102 and rifampin is being compared to the standard-of-care i.v. antibiotic therapy for the treatment of infected hip and knee joints after joint replacement surgery (http://www.clinicaltrials.gov).

Pleuromutilins

The diterpene antibiotic pleuromutilin was first discovered as a natural product in 1951 (113); however, modest antibacterial activity against Gram-positive bacteria and weak *in vivo* activity initially prevented further development of this compound for human clinical use (114). Pleuromutilin inhibits bacterial protein synthesis by selectively binding to prokaryotic ribosomes with no effect on eukaryotic protein synthesis (115). This unique mechanism of action also results in a lack of cross-resistance to most marketed antibiotics and has thus inspired analog efforts in an attempt to find clinically desirable derivatives. Efforts at Sandoz to further improve the antimicrobial activity led to a series of new derivatives synthesized between 1963 and 1966, and further work led to the development of the first veterinary pleuromutilin, tiamulin, which was approved in 1979 (118). After failure to overcome issues such as metabolic stability, oral bioavailability, toxicity, modest antibacterial activity, and chemical tractability, retapamulin in 2007 became the first pleuromutilin approved for human indications following its successful development for topical use by GlaxoSmithKline (118–120).

BC-3781. Chemical SAR from >1,000 pleuromutilin derivatives led to the discovery of BC-3781 (Nabriva Therapeutics) (Fig. 3, compound 13) in 2006. It exhibits antibacterial activity against Gram-positive pathogens, atypical pathogens, and fastidious Gram-negative pathogens and is especially active against MDR pathogens, including MRSA, MDR *S. pneumoniae*, and vancomycin-resistant *E. faecium* (121, 122). MIC_{90} values were reported as follows: MRSA, 0.25 μg/ml; coagulase-negative staphylococci, 0.12 μg/ml; beta-hemolytic streptococci, 0.06 μg/ml; viridans group streptococci, 0.5 μg/ml; and *E. faecium* (including vancomycin-nonsusceptible strains), 2 μg/ml. Most importantly, it displays favorable PK/PD parameters that allow systemic administration. BC-3781 was shown to have *in vivo* efficacy in stringent infection models of skin disease, pneumonia (MRSA and *S. pneumoniae*) and bacteremia. In 2011, Nabriva reported the results of a successful clinical phase 2 trial using i.v. BC-3781. This was a double-blind randomized trial enrolling 207 patients with ABSSSI, and the efficacy of BC-3781 (100 or 150 mg every 12 h [q12h]) was compared with that of vancomycin (1,000 mg q12h) for 5 to 14

days (123; http://www.nabriva.com). *S. aureus* was the predominant pathogen (in 95.1% of patients with a baseline pathogen), and 74.1% of the strains were MRSA. Clinical cure rates in clinically evaluable patients were 90.0% and 88.9%, respectively, for 100 and 150 mg BC-3781 and 92.2% for vancomycin. More drug-related adverse events were reported in vancomycin-treated patients than in those receiving BC-3781 (123).

BC-7013. Nabriva is also advancing a pleuromutilin, BC-7013 (Fig. 3, compound 14), for topical use. This compound reportedly has potent antibacterial activity against resistant Gram-positive pathogens, including MRSA, with MIC_{90} values of ≤0.06 μg/ml against staphylococci and streptococci; it also has encouraging PK/PD parameters in skin. It is being developed for several bacterially associated or derived dermatological diseases (124; http://www.nabriva.com). Phase 1 results indicated good tolerability of topical formulations and no systemic exposure.

AN3365

Scientists at Anacor identified the protein synthesis inhibitor AN3365 (GSK2251052, GSK'052), a novel oxaborole-containing inhibitor of leucyl-tRNA synthetase that was being codeveloped by GlaxoSmithKline. AN3365 exhibited potent activity against Gram-negative bacteria, with MIC_{90} values of 1 and 4 μg/ml against drug-resistant *Enterobacteriaceae* and *P. aeruginosa*, respectively (10). However, the drug selected for resistance in the laboratory at rates of 10^{-7} to 10^{-8} (10). Following successful completion of phase 1 trials, phase 2 clinical trials were terminated somewhat abruptly after several patients developed resistant bacteria during treatment for cUTI (http://anacor.com/gsk052.php). Further development was transferred back to Anacor.

NOVEL β-LACTAMS AND β-LACTAMASE INHIBITOR COMBINATIONS

β-Lactam antibiotics have been used therapeutically for the past 70 years to treat a wide range of disease states, from mild community-acquired respiratory infections to life-threatening nosocomial pneumonia. These bactericidal, safe, and efficacious agents act by inhibiting essential cell wall-synthesizing enzymes, the penicillin-binding proteins (PBPs), with no mammalian homologs. Although new β-lactam-containing analogs have populated the pharmaceutical pipeline for many years, few new β-lactams have recently entered clinical trials as sole agents. This may be due largely to the proliferation of β-lactamases, the ubiquitous β-lactam-inactivating proteins that now number more than 1,300 unique enzymes (125), thereby rendering most β-lactams labile to hydrolysis by at least some subset of β-lactamases. It is not surprising, therefore, that most of the interest in β-lactams resides in novel β-lactam–β-lactamase inhibitor combinations, as seen in the agents described below.

BAL30072. The siderophore-substituted monosulfactam BAL30072 (Fig. 4, compound 1) from Basilea Pharmaceutica International is a monocyclic β-lactam that is in phase 1 clinical trials (126). BAL30072 exhibits *in vitro* activity against *Enterobacteriaceae* similar to that of other monocyclic β-lactams, including against strains that produce MBLs (127). It is distinguished by its potent activity against many strains of nonfermenters, including MBL-producing strains of *P. aeruginosa* and *Acinetobacter* (128, 129). This activity is attributed to its stability to hydrolysis by MBLs, as well as its high affinity for binding to both PBP 1a and PBP 1b and to the classical monobactam target of PBP 3. Unexpectedly, *E. coli* cells underwent spheroplasting prior to lysis, in contrast to the filamentation usually observed with monobactams due to their preferential binding to PBP 3 (127). Entry into Gram-negative bacteria is facilitated by the dihydropyridone moiety, which utilizes the bacterial iron uptake system to cross the bacterial outer membrane (127). Siderophore conjugates in the past have experienced a high rate of resistance development due to selection of mutations in TonB or other proteins associated with iron transport systems (130, 131). At this time, it appears that BAL30072 has much lower rates of resistance selection than those described for previous siderophore conjugates, with most mutations observed in β-lactamase-related activities rather than in iron transport genes (126). Because of the lability of this molecule to occasional β-lactamases (128), it is possible that optimal therapeutic use of this monosulfactam will be in combination therapy. Preclinical studies of a BAL30072-meropenem combination have demonstrated good synergy of the two β-lactams both in time-kill studies *in vitro* and in a rat soft tissue *in vivo* infection using five strains of MDR *A. baumannii* (129); the combination has also been reported to demonstrate efficacy in mouse thigh infections caused by Gram-negative bacteria producing extended-spectrum β-lactamases (ESBLs) or the metallo-carbapenemase NDM-1 (132).

β-Lactamase Inhibitor Combinations

Penicillins combined with the β-lactamase inhibitor clavulanic acid, sulbactam, or tazobactam have been used successfully for over 30 years in both oral and parenteral therapies. The major targets for these agents are class A β-lactamases, particularly those in functional groups 2a and 2b, which are inactivated by the various inhibitors in multipathway reaction sequences (133–135). Although these inhibitor combinations have selected few novel β-lactamase-related mutations compared to the large number of β-lactamase variants selected by single β-lactams (125), resistance continues to plague these useful combinations. New β-lactamases with low affinity for the inhibitors have emerged, greater numbers of β-lactamases intrinsically unresponsive to the inhibitors are being produced, and larger numbers of β-lactamases from different functional groups are identified in a single clinical isolate. These factors all suggest that new inhibitor combinations may be useful for the treatment of infections caused by highly resistant β-lactamase-producing bacteria.

Ceftolozane-tazobactam. Ceftolozane (CXA-101, FR264205; Cubist) (Fig. 4, compound 2) is a 3′-aminopyrazolium cephalosporin with a reported MIC_{90} of 1 μg/ml against a set of *P. aeruginosa* isolates with ceftazidime, imipenem, or ciprofloxacin MICs 8- to 16-fold higher (136). Ceftolozane was originally identified by scientists at Astellas Pharma and licensed to Calixa, which was acquired by Cubist, which has now acquired the global rights to develop, manufacture, and commercialize ceftolozane-tazobactam (http://www.cubist.com/news/94-cubist_obtains_remaining_rights_to_ceftolozane_from_astellas) (Fig. 4, compound 3). Although ceftolozane was shown to be vulnerable to hydrolysis by ESBLs, AmpC cephalosporinases, and KPC β-lactamases, the addition of 4 μg/ml of tazobactam to the cephalosporin to create CXA-201 decreased ceftolozane MICs to 8 μg/ml for 76% of ESBL producers; few of the AmpC- or KPC-producing isolates responded to the inhibitor combination (137). The combination was especially effective against *E. coli* isolates producing either a CTX-M-14 or a CTX-M-15 ESBL, the two most commonly encountered ESBLs worldwide,

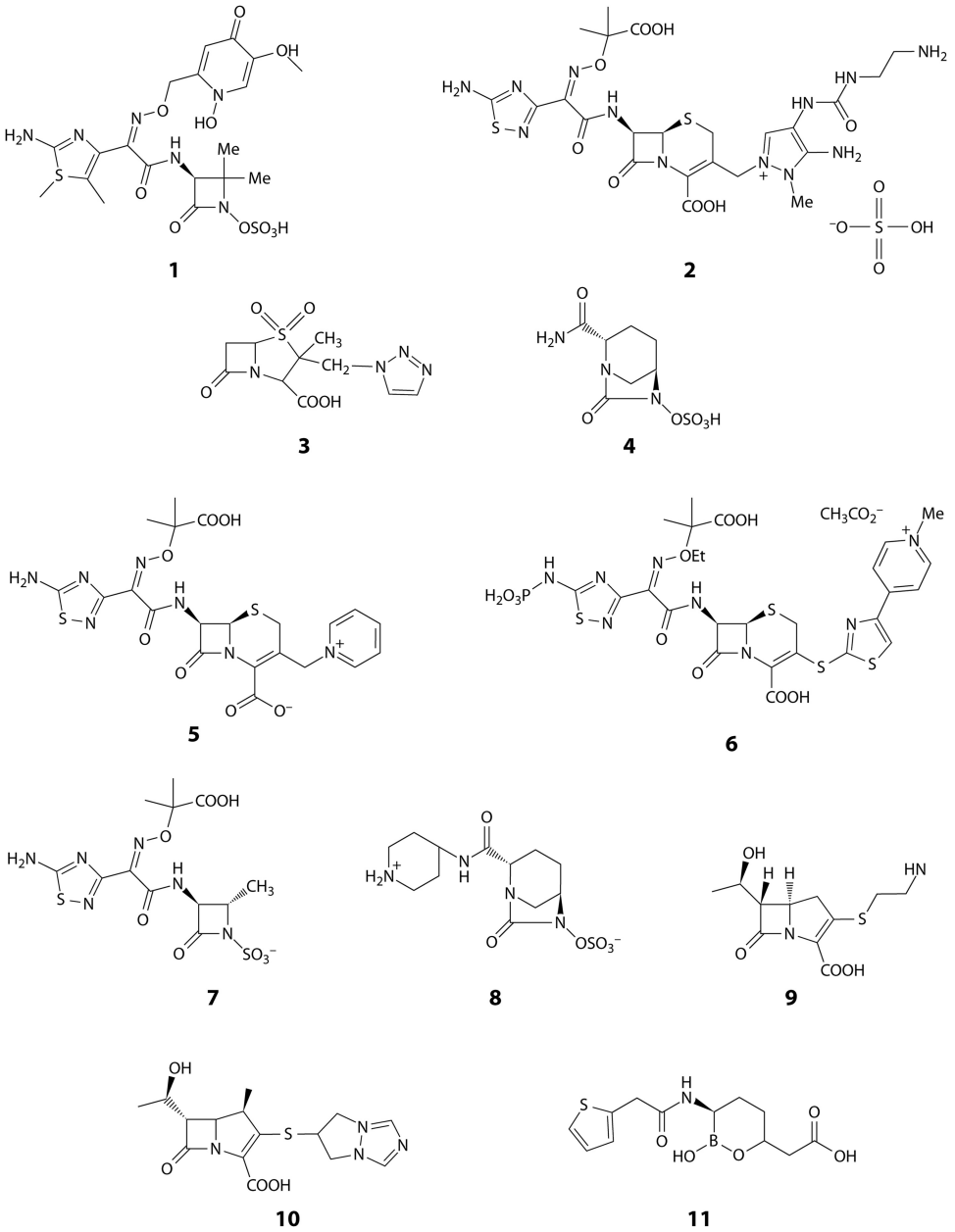

FIG 4 Structures of recent investigational β-lactam-containing agents. 1, BAL30072; 2, ceftolozane; 3, tazobactam; 4, avibactam; 5, ceftazidime; 6, ceftaroline; 7, aztreonam; 8, MK-7655; 9, imipenem; 10, biapenem; 11, RPX7009.

although maximal activity was achieved using 8 μg/ml of tazobactam rather than 4 μg/ml as in previous studies (138).

Because a major strength will be the treatment of infections caused by MDR *P. aeruginosa*, much attention has been paid to resistance mechanisms for ceftolozane in this organism. Common resistance factors for the antipseudomonal drugs imipenem and ceftazidime such as derepressed AmpC production, the loss of the OprD porin, or upregulated efflux did not cause ceftolozane MICs to rise above 4 μg/ml. However, the acquisition of β-lactamases such as MBLs or PER or OXA ESBLs resulted in ceftolozane MICs of >32 μg/ml (139). CXA-201 has completed two phase 2 trials for treatment of cIAI and cUTI and is currently in phase 3 clinical trials for cIAI and cUTI caused by selected Gram-negative bacteria, including multidrug-resistant *P. aeruginosa*, with a phase 3 trial for ventilator-associated bacterial pneumonia expected to begin in mid-2013. The FDA has designated CXA-201 a qualified infectious disease product for all three indications; the cIAI indication has also been granted fast track status (http://www.cubist.com/products/cxa_201).

Avibactam combinations. Avibactam (NXL104; AstraZeneca) (Fig. 4, compound 4) was initially characterized by scientists from Novexel as a non-β-lactam bicyclic diazabicyclooctane with inhibitory activity against class A and class C β-lactamases in 1:1 stoichiometric ratios (140). Initial mechanistic studies described the inhibitor as an irreversible inactivator with high carbamylation rates and very slow decarbamylation, with a rate constant

close to zero for the class A TEM-1 and class C P99 enzymes (140). However, using assay conditions under which lower concentrations of the enzyme-inhibitor complex were allowed to equilibrate over a longer time period, later studies suggested reversible covalent binding to the class A TEM-1, CTX-M-15, and KPC-2 enzymes and also to the AmpC and P99 cephalosporinases (141). Exchange of the inhibitor between acyl and apo forms of various enzymes, e.g., avibactam–acyl-TEM-1 and apo-CTX-M-15, was demonstrated using mass spectrometry. This mechanism is unique for β-lactamase inhibitors and may translate into better clinical efficacy, as there is no depletion of inhibitor before enzyme inhibition as seen with clavulanic acid or tazobactam (133, 134). However, sufficient inhibitor must be used to saturate all the β-lactamases found in the disease-causing pathogens. When assessing the antimicrobial activity of avibactam combinations, it is important to note the modest antibacterial activity of avibactam itself, which demonstrated MIC values of 8 to 16 μg/ml against 292 strains of ESBL- and AmpC-producing *Enterobacteriaceae* (142). In 2009, AstraZeneca acquired Novexel and announced an agreement to collaborate with Forest Laboratories for codevelopment and commercialization of the combinations ceftazidime-avibactam and ceftaroline fosamil-avibactam.

Ceftazidime-avibactam. The ceftazidime-avibactam combination (CAZ-AVI) (AstraZeneca) (Fig. 4, compounds 5 and 4, respectively) demonstrated potentially useful antimicrobial activity against recent isolates of *Enterobacteriaceae* that produce the KPC carbapenemase, as described in some of the earliest descriptions of the inhibitor (143–145). MICs for ceftazidime (Fig. 4, compound 5) in the presence of 4 μg/ml avibactam were no higher than 4 μg/ml when tested against most KPC-, ESBL-, and AmpC-producing *Enterobacteriaceae*, with the exception of a few isolates of *Enterobacter aerogenes* that coproduced KPC and AmpC enzymes together with loss of a porin (142, 143, 146). Activity against many strains of OXA-48-producing *K. pneumoniae* has also been reported (146, 147). *In vitro* microbiological activity of the combination against *P. aeruginosa* indicated MIC_{50} values of <8 μg/ml across several studies (148–150), with 94% of the isolates from a Canadian study being susceptible to ceftazidime in the presence of 4 μg/ml of avibactam (150). Notably, the combination has no useful activity against bacteria that produce MBLs (146). The combination is currently in phase 3 clinical trials to assess safety and efficacy for treatment of cIAI, cUTI, and nosocomial pneumonia (http://www.clinicaltrials.gov). In addition, it is being studied in phase 3 trials for the treatment of infections caused by any ceftazidime-resistant Gram-negative pathogens across therapeutic indications, using a novel approach to the development of β-lactamase inhibitors.

Ceftaroline-avibactam. Ceftaroline (Forest) (Fig. 4, compound 6) is an anti-MRSA cephalosporin with high affinity for binding to PBP 2a (2′) from MRSA and to PBP 2x in *S. pneumoniae*, resulting in potent activity against staphylococci and streptococci, both *in vitro* and *in vivo* (151, 152). Its utility in the *Enterobacteriaceae* is limited by its susceptibility to hydrolysis by AmpC cephalosporinases, ESBLs, and both serine and metallocarbapenemases (153) and by its intrinsic low activity in nonfermentative bacteria (154). The prodrug ceftaroline fosamil has been approved by the FDA for treatment of ABSSSI and CABP (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo), indications in which Gram-positive staphylococci and streptococci predominate.

Addition of avibactam to ceftaroline provides a broad-spectrum antibacterial activity that is similar to that of the ceftazidime-avibactam combination with two main exceptions: MRSA is added to the spectrum, but only very limited activity against *P. aeruginosa* is observed (155). The Gram-negative antibacterial activity of ceftaroline is thereby expanded to include most enteric bacteria, with ceftaroline MIC_{90} values of <1 μg/ml against *Enterobacteriaceae* producing class A and class C β-lactamases (153, 155). As with other penicillin and cephalosporin β-lactamase inhibitor combinations, the addition of the inhibitor does not enhance activity if an MBL is produced (153, 155). Single-step resistance selection by the ceftaroline-avibactam combination occurred at a low frequency ($<10^{-9}$) in three enteric bacterial strains (156). Of the three stable mutants that were isolated, one *E. coli* strain produced a CTX-M-15 variant with a Lys237Gln substitution. Interestingly, this mutant became more sensitive to ceftaroline (the MIC decreased from >64 to 32 μg/ml) alone, whereas ceftaroline MICs in the combination increased from <0.06 to 8 μg/ml in the presence of 4 μg/ml avibactam. Two *Enterobacter cloacae* strains with derepressed AmpC cephalosporinases and porin defects were selected by the inhibitor combination; in these, ceftaroline exhibited 16- to 64-fold increases in MICs when tested with 4 μg/ml avibactam (156). These mutations appear to be similar to what can be expected by selection with oxyimino cephalosporins (157), but the AmpC enzymes in both strains exhibited identical deletions of amino acids 213 to 226, an unusual mutation that may bear watching in the future. A phase 2 clinical trial has been completed in which the ceftaroline-avibactam combination was compared to doripenem in patients with cUTI (http://www.clinicaltrials.gov).

Aztreonam-avibactam. Because monobactams are hydrolyzed by ESBLs but are inherently stable to hydrolysis by MBLs, Livermore and colleagues suggested that an avibactam-aztreonam (AVI-ATM) (AstraZeneca) (Fig. 4, compound 7) combination might be inhibitory to MBL-producing pathogens (146). In a study of carbapenemase-producing *Enterobacteriaceae*, aztreonam had MICs of <4 μg/ml in combination with 4 μg/ml avibactam, including strains that produced OXA-48, serine carbapenemases, or MBLs (146). When the aztreonam-avibactam combination was tested against 126 *P. aeruginosa* isolates, aztreonam tested as resistant for 27.8% of the isolates, compared to 1.6% of the isolates that were resistant to a ceftazidime-avibactam combination (150). This suggests that the ceftazidime combination would be preferable against non-MBL-producing pseudomonal isolates. AstraZeneca has initiated a phase 1 clinical trial of avibactam combined with aztreonam (http://www.clinicaltrials.gov). In July 2013 the European Innovative Medicines Initiative announced a call for proposals to establish a public-private collaboration to develop and conduct phase IIa and phase III therapeutic trials for this avibactam combination (http://www.imi.europa.eu/content/stage-1-7).

Imipenem–MK-7655. MK-7655 (Merck) (Fig. 4, compound 8) is a non-β-lactam bicyclic diazabicyclooctane that was introduced by Merck scientists in 2010 (158). This inhibitor resembles avibactam in structure, but its synthesis has been streamlined, leading to the facile production of clinical supplies (159). It has potent inhibitory activity similar to that of avibactam against class A and class C β-lactamases (158). Time-kill studies demonstrated synergy between MK-7655 and imipenem (Fig. 4, compound 9) when tested against KPC-producing *K. pneumoniae* and carbapenem-

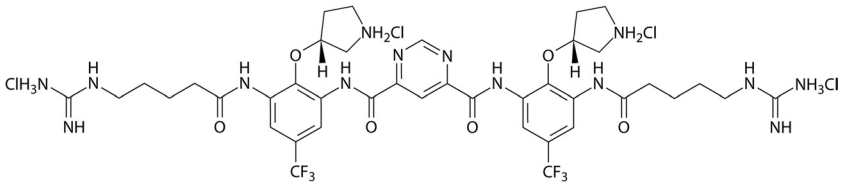

FIG 5 Structure of the investigational peptide mimetic brilacidin.

resistant strains of *P. aeruginosa* strains with OprD porin deletions and overexpression of AmpC (160). Pharmacodynamic studies have helped to guide the clinical dosing of the inhibitor combination based on a new modeling index of fluctuating susceptibility over time, defined as time above instantaneous MIC ($T>MIC_i$) (161). According to this parameter, a value of 69% $T>MIC_i$ resulted in comparable killing of a KPC-2-producing *K. pneumoniae* strain when tested at escalating doses of imipenem–MK-7655. The combination is currently in phase 2 clinical trials for treatment of cIAI and cUTI (http://www.clinicaltrials.gov).

Biapenem-RPX7009. The biapenem-RPX7009 (Rempex) (Fig. 4, compounds 10 and 11) combination is the only investigational β-lactamase inhibitor combination that is composed of two novel agents that have not been approved by the FDA. Biapenem ("RPX-2003") is a broad-spectrum carbapenem with *in vitro* activity against Gram-negative and Gram-positive bacteria similar to that of meropenem (162, 163). Like other carbapenems, biapenem is not affected by the presence of ESBLs but is labile to hydrolysis by both serine and metallo-carbapenemases (164). Although carbapenem resistance is increasing, >75% of recent Japanese pseudomonal isolates were susceptible to biapenem and meropenem (165). Pharmacologically, biapenem is notable for its low proconvulsive activity compared to that of imipenem (166). Biapenem was approved in Japan in 2001 (http://www.kegg.jp/dbget-bin/www_bget?dr:D01057) and is currently used in many Japanese nosocomial settings.

In 2012 Rempex revealed the novel structure of RPX7009, a boronic acid-containing β-lactamase inactivator (167) with inhibitory activity against class A and class C serine β-lactamases, particularly highlighting both *in vitro* and *in vivo* activity against KPC-producing *K. pneumoniae* (168, 169). Boronic acid inhibitors of PBPs (170) and of classes A, C, and D β-lactamases had previously been identified (171–173), but none has achieved success as a clinical candidate. Preclinical testing of RPX7009 indicated that the inhibitor had no off-target effects, and it was well tolerated at high doses, with no safety signals that would preclude future development (174). A phase 1, randomized, double-blind, placebo-controlled, ascending-single- and -multiple-dose study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of i.v. biapenem (RPX2003) and RPX7009 dosed singly and in combination in healthy human subjects is currently in progress (http://www.clinicaltrials.gov).

MEMBRANE-ACTING AGENTS

Since the isolation of magainins from the skin of frogs in 1987 (175), researchers have attempted to further advance antimicrobial peptides (AMPs) as therapeutic agents. However, despite more than 2 decades of effort, no peptide antibiotics have yet reached the market. AMPs possess several attractive properties, including broad-spectrum antibacterial activity, mechanisms of action that differ from those of current antibiotics, rapid bactericidal effects, and often a greatly reduced propensity to select for resistant mutants (176). In most cases, host defense proteins kill bacteria by forming pores in bacterial cell membranes. However, there have also been a number of roadblocks to date in the development of drug candidates. These include toxicity in the host, rapid *in vivo* clearance often due to protease susceptibility, poor bioavailability, and problems with drug substance production, including a relative high cost of goods (176, 177).

Brilacidin. A number of mimics of AMPs, both peptidic and nonpeptidic, have been investigated for their potential as therapeutic drug candidates. The purpose of such mimics is to derive compounds that could maintain the amphiphilic properties of naturally occurring AMPs while solving obstacles mentioned above that have prevented peptide-based antimicrobials from thus far reaching the market as antimicrobial agents. One approach has been to use chemical mimics, i.e., arylamide foldamers, consisting of an arylamide backbone and various charged groups, as exemplified by brilacidin (PMX-30063; Polymedix, Inc.) (Fig. 5), a peptidomimetic lead compound being developed for the treatment of *S. aureus* infections (178). The reported MIC_{90} against 263 *S. aureus* isolates tested was 1 μg/ml, with an MIC range of 0.5 to 2 μg/ml, and only 2.7% of the strains exhibited an MIC of 2 μg/ml (179). Bactericidal activity was not affected by the presence of 50% human serum. PMX-30063 recently completed a phase 2 clinical trial to treat patients with ABSSSI infections caused by *S. aureus* and demonstrated clinical efficacy and safety in all evaluated doses, although 65 to 87% of the treated patients exhibited numbness and tingling (http://www.polymedix.com). Polymedix planned to initially seek FDA approval for an i.v. formulation of brilacidin in treating patients with ABSSSI and then to perform additional clinical studies in patients with other infections, such as bloodstream infections, lung infections, and oral mucositis (http://www.polymedix.com). Polymedix has had recent financial difficulties, and the continued development of this compound is now unclear (http://www.fiercebiotech.com/story/polymedix-defaults-and-hands-over-phii-antibiotic-bankruptcy-court/2013-04-02).

POL7080. POL7080 from Polyphor (structure unavailable) is a protein epitope mimetic (PEM) under development for the treatment of *P. aeruginosa* infections (http://www.polyphor.com). It was found to have a novel, non-membrane-lytic mechanism of action, with the cellular target identified as a homolog of the beta-barrel protein LptD (Imp/OstA), which functions in outer membrane biogenesis (180, 181). POL7080 is a lead compound derived from a series of macrocyclic β-hairpin mimetics of the cationic antibacterial peptide protegrin-1 optimized to improve antibacterial activity, decrease cytotoxic hemolytic activity, and improve plasma stability. This compound was active in the nanomolar range against *Pseudomonas* spp. (MIC_{90} of 0.13 μg/ml) but was largely inactive against other Gram-negative and Gram-positive

bacteria. In addition, POL7080 showed *in vivo* efficacy in mouse septicemia and lung and thigh infection models. In a phase 1 clinical trial in healthy volunteers, single doses were well tolerated at plasma concentrations expected to meet or exceed efficacious levels, with no serious adverse events reported (182).

ACHN-975. Achaogen (http://www.achaogen.com/pipeline/lpxc) is developing novel antibiotics that inhibit outer membrane biosynthesis via a previously unexploited target, LpxC. ACHN-975 (structure unavailable) represents a first-in-class agent with a novel mechanism of action with good antibacterial activity (MIC of <1 μg/ml) against a broad spectrum of MDR Gram-negative bacteria, including *E. coli* and *P. aeruginosa*, with no preexisting clinical resistance. ACHN-975 has completed a phase 1 double-blind, randomized, placebo-controlled, single-ascending-dose study to assess safety, tolerability, and PK and recently terminated a phase 1 multiple-dose study. (http://www.clinicaltrials.gov).

AGENTS ACTIVE AGAINST GRAM-POSITIVE BACTERIA

Agents demonstrating activity only against Gram-positive bacteria are perceived to be of a lower medical priority, due to the alarming increase in resistance observed in MDR Gram-negative pathogens and the relative success of efforts to fill the pipeline when MRSA was recognized as a growing problem (183). Resistance to newer anti-Gram-positive agents such as linezolid and daptomycin that are used to treat infections caused by multidrug-resistant staphylococci and enterococci is still low; susceptibility to these agents has been documented over the period of 2003 to 2009 as ≥99.5% against large groups of surveillance isolates, including MRSA and VRE (184, 185). However, daptomycin nonsusceptibility is being reported to be as high as 38% in Australian vancomycin-intermediate *S. aureus* (VISA) strains (186) and 9% to 15% in hetero-VISA (hVISA) isolates from the United States and Australia, respectively (186, 187); for VRE, a major cancer center reported a surge in daptomycin-resistant isolates from 3.4% in 2007 to 15.2% in 2009 (185). According to a recent surveillance study in 61 U.S. medical centers, low linezolid resistance was seen, with rates of 0.06% in *S. aureus*, 1.5% in coagulase-negative staphylococci, and 0.75% in the enterococci, but resistance still exists (188). Although it appears that there are still effective agents to treat resistant Gram-positive cocci, experience tells us that this condition will not continue, and new agents in new classes will be needed in the future.

Glycopeptides

Dalbavancin and oritavancin. Dalbavancin (Durata) (Fig. 6, compound 1) (189) and oritavancin (The Medicines Company) (Fig. 6, compound 2) (190), two (lipo)glycopeptides developed to treat MDR Gram-positive bacteria, have been in the antibiotic pipeline for over a decade (191). The glycopeptides, including vancomycin, block the transglycosylation of peptidoglycan biosynthesis by sequestering the substrates, thereby disrupting bacterial cell wall formation. Dalbavancin has potent antistaphylococcal activity, with MIC_{90} values of 0.25 to 05 μg/ml against isolates that include MRSA and one vancomycin-resistant strain (192), as well as vancomycin-susceptible enterococci; in contrast, oritavancin has up to 8-fold-higher MICs than dalbavancin, but generally at least 2-fold-lower MICs than vancomycin, against the staphylococci (191). Oritavancin includes additional enterococci in its spectrum, including Van(A)-containing VRE, unlike dalbavancin, which has poor activity against these bacteria, thus bringing into question the activity of dalbavancin against Van(A)-producing staphylococci (191, 193). Because of the strong dimerization of oritavancin, which differs from the case for vancomycin and dalbavancin, cooperative interactions can occur between the dimerized glycopeptide and the cytoplasmic membrane to which it can be anchored, providing additional potency (194). Both drugs have long half-lives in humans and can be dosed at intervals less frequently than once a day; dalbavancin, with a half-life of up to 258 h, may be dosed weekly, whereas oritavancin, with a half-life of 393 h, may be effective after a single dose (195). A recent phase 2 study demonstrated that a single 1,200-mg dose of oritavancin was as effective as daily dosing of 200 mg per day for 3 to 7 days (196).

Dalbavancin, acquired by Pfizer via Vicuron, has completed 15 clinical studies, including phase 3 trials for treatment of skin and skin structure infections; however, the FDA issued an approvable letter in 2007 (http://www.reuters.com/article/2007/12/24/idUSN2127847620071224) with a request for additional clinical studies using an updated study design (79). After Pfizer ceased development of the drug and transferred dalbavancin to Durata Therapeutics, the drug has completed two additional phase 3 trials in ABSSSI (http://www.clinicaltrials.gov) based on the 2010 FDA guidance; the company may file for approvals by both the FDA and the European Medicines Agency in 2013 (http://www.duratatherapeutics.com/product-pipeline/dalbavancin/clinical-trials).

Following the out-licensing of oritavancin from Eli Lilly to InterMune and then to Targanta, clinical trials were completed and an NDA was reviewed by the FDA and an Anti-Infectives Drug Advisory Committee in 2008. The FDA declined to approve the drug due to concerns about trial design and clinical data that contained too few current MRSA isolates. The Medicines Company acquired the drug and has conducted two additional ABSSSI trials, with the intention of filing an NDA by the end of 2013. Results from both trials met all protocol-specified endpoints showing that a single oritavancin dose was noninferior to twice-a-day dosing of vancomycin for 7 to 10 days (http://ir.themedicinescompany.com/phoenix.zhtml?c=122204&p=irol-newsArticle&ID=1834647&highlight=).

PDF Inhibitors

Peptide deformylase (PDF) is a novel target for antibacterial drugs, with no drugs having progressed into full clinical development until very recently. The mechanism of action of this metalloenzyme in eubacteria begins with the addition of *N*-formylmethionine during peptide synthesis, with sequential posttranslational removal of the *N*-formyl group by PDF followed by methionine aminopeptidase (MAP)-catalyzed methionine removal (197). PDF is an essential bacterial enzyme exhibiting different molecular structures among bacterial species (198, 199). Up to four PDF sequences have been identified in a single species, with low sequence identity often observed among PDF enzymes in different bacterial strains (198). Although nonessential homologs have been identified in animal mitochondria (200), protein structures are deemed to be sufficiently different across the kingdoms so that high selectivity can be anticipated from inhibitors of the bacterial enzyme (201). The first PDF inhibitor described from pharmaceutical screening was actinonin, from Versicor in 2000 (197).

GSK1322322. GSK scientists selected PDF as one of their 67 targets for high-throughput screening (HTS) assays in the 1990s,

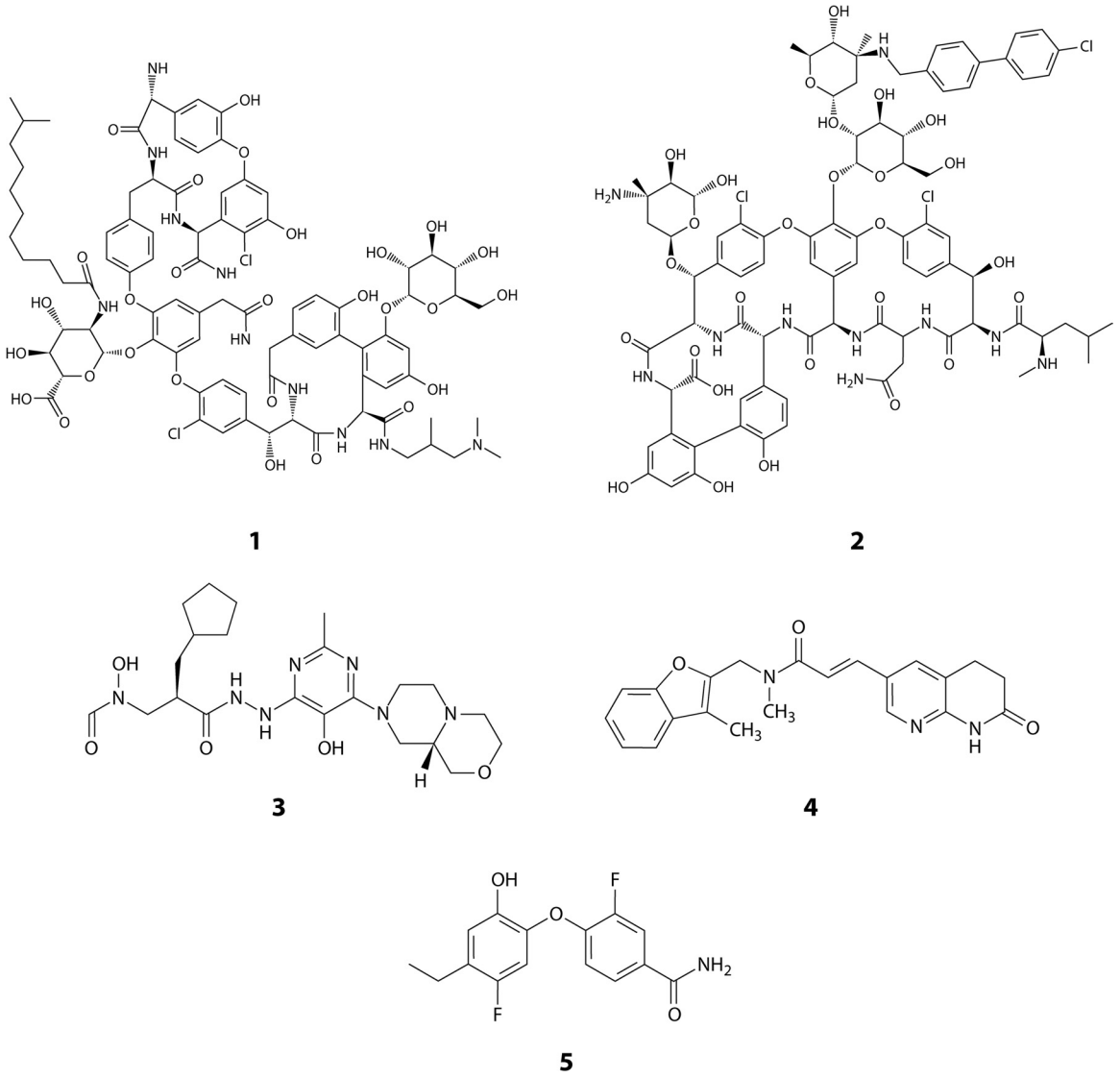

FIG 6 Structures of investigational agents with activity against Gram-positive bacteria. 1, dalbavancin; 2, oritavancin; 3, GSK1322322; 4, AFN-1252; 5, MUT056399.

leading to one of the three screening campaigns that actually yielded a "druggable" lead compound (202). GSK is currently developing the novel hydrazinopyrimidine inhibitor GSK1322322 (Fig. 6, compound 3), the first PDF inhibitor that has advanced through phase 2 clinical trials (http://www.clinicaltrials.gov). Although early PDF inhibitors were recognized particularly for their microbiological activity against staphylococci, especially MRSA (203), GSK1322322 also may have useful activity against *S. pneumoniae* and *H. influenzae*, with MICs of ≤4 μg/ml against these organisms in addition to drug-resistant staphylococci (204, 205). Clinical studies in healthy subjects showed good penetration of the inhibitor into epithelial lining fluid and alveolar macrophages (206). Thus, the *in vitro* microbiological profile and bioavailability in the lung support clinical studies of this drug in respiratory disease. Phase 3 trials in Europe for the treatment of ABSSSI and CABP are being implemented through the Innovative Medicines Initiative COMBACTE (http://www.imi.europa.eu/content/combacte).

Fatty Acid Synthesis Inhibitors

Like for the PDF inhibitors, no drug targeting fatty acid biosynthesis has been developed into an approved antibacterial drug outside the mycobacterial arena, although several research groups have conducted screening campaigns using this as a target (207–211). At GSK, lead compounds were identified from HTS assays for two enzymes involved in fatty acid biosynthesis: FabH, the β-ketoacyl-acyl carrier protein synthase III, and the enoyl-acyl carrier protein (ACP) reductase FabI (202). Bacterial FabI, with little sequence homology to corresponding mammalian enzymes (212), is an essential enzyme that catalyzes the reduction of *trans*-2-enoyl-ACP to acyl-ACP in the final rate-limiting step of the elongation cycle in fatty acid biosynthesis (213). It should be noted that not all bacterial enzymes with enoyl-acyl carrier protein reductase activity are closely related to the single copy of FabI that is the potential drug target in *S. aureus*. In *S. pneumoniae* the FabK enzyme has that functionality (202), so that targeting the

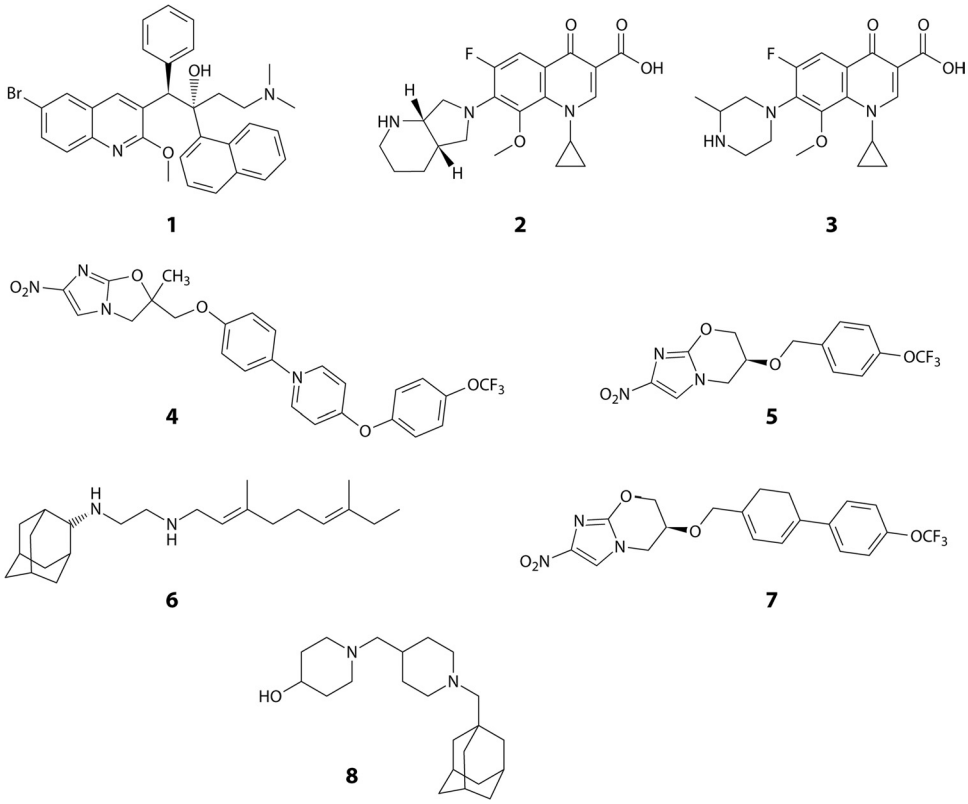

FIG 7 Structures of investigational agents with activity against *Mycobacterium tuberculosis*. 1, bedaquiline; 2, moxifloxacin; 3, gatifloxacin; 4, delamanid; 5, PA-824; 6, SQ-109; 7, TBA-354; 8, SQ-609.

staphylococcal reductase could result in a narrow-spectrum drug with utility only against *S. aureus*, including MRSA. Although FabI is also the target for triclosan, the broad-spectrum biocide, selective FabI inhibitors that are active against triclosan-resistant *S. aureus* strains have been identified (207).

AFN-1252. Scientists from Affinium Pharmaceuticals have described an iterative structure-guided chemistry program targeting FabI from *S. aureus* (214, 215) from which they subsequently identified AFN-1252, a 3-methylbenzofuran linked to an oxotetrahydronaphthyridine by an *N*-methylpropenamide (216) (Fig. 6, compound 4). This specific antistaphylococcal inhibitor of FabI had MIC values of ≤0.12 μg/ml against all clinical isolates of *S. aureus* ($n = 502$) and *Staphylococcus epidermidis* ($n = 51$) tested, including methicillin-resistant strains. Poor activity was reported against streptococci, enterococci, and Gram-negative isolates, with MIC_{90} values of >4 μg/ml (216). Biochemical, structural, and microbiological studies confirmed that fatty acid biosynthesis was the killing target for the compound (217). A phase 2 clinical trial for oral therapy of ABSSSI in the outpatient setting was recently completed, with favorable outcomes observed for safety and efficacy; acceptable tolerability was reported, although 67% of the patients suffered some kind of adverse effect, with 4 of 103 patients withdrawing due to drug-related treatment-associated adverse events (http://afnm.com/news/affinium-news-032013.htm). Future clinical experience will be needed to determine the role for this novel agent.

MUT056399. The FabI inhibitor MUT056399 (FabPharma) (Fig. 6, compound 5) has potent antistaphylococcal activity, with MIC_{90} values of 0.03 to 0.12 μg/ml against *S. aureus* and 0.12 to 4 μg/ml against coagulase-negative staphylococci (218). It was shown to be specific for inhibition of FabI in *S. aureus* and *E. coli* but did not inhibit the FabK homologs from other Gram-positive bacteria. While the frequency of resistance selection *in vitro* was low, it resulted in two *S. aureus* populations of FabI mutants, leading to low and high resistance (MICs of 0.5 to 4 μg/ml and >32 μg/ml, respectively) (210). In 2010, results from a phase 1 ascending-dose study in healthy human volunteers indicated an elimination half-life of approximately 1 h (218). The development status of the agent is uncertain, as it is currently not in clinical trials in the United States (http://www.clinicaltrials.gov).

ANTITUBERCULOSIS DRUGS

Although few new antibacterial agents have reached the marketplace over the past 30-plus years, one area for some optimism is the antituberculosis (anti-TB) drug pipeline (219, 220). Probably due to the emergence of MDR strains of *Mycobacterium tuberculosis* over the past 2 decades, there has been much research activity, and this has led to the recent approval of the first new TB drug in 40 years, bedaquiline (TMC207, R207910; from Janssen Therapeutics, the pharmaceuticals unit of Johnson & Johnson) (Fig. 7, compound 1) (FDA Press Release http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm), as part of combination therapy to treat adults with multidrug-resistant pulmonary tuberculosis when other alternatives are not available. The drug is currently being studied to confirm its safety in extended clinical trials and is under development for the treat-

ment of drug-susceptible tuberculosis. Several other promising drugs at various stages in clinical development are described below. A current summary of the TB drug pipeline can be found on the website of the Global Alliance for TB Drug Development (http://www.tballiance.org).

Moxifloxacin and gatifloxacin. The fluoroquinolones moxifloxacin and gatifloxacin (Fig. 7, compounds 2 and 3) were marketed in 1999 for respiratory infections and displayed improved Gram-positive antibacterial activity over those of ciprofloxacin and levofloxacin (221). It was subsequently discovered that these compounds also had improved anti-TB activity compared with older quinolones (222, 223). Interestingly, *M. tuberculosis* has not been found to possess any type IV topoisomerase; therefore, fluoroquinolones likely specifically inhibit the mycobacterial DNA gyrase (224). This raises the possibility of further optimization of topoisomerase inhibitors with improved inhibition of the mycobacterial gyrase enzyme. Gatifloxacin was reported to be slightly more active against *M. tuberculosis* clinical isolates than moxifloxacin, with an MIC_{90} range of 0.007 to 0.12 μg/ml reported for gatifloxacin and 0.031 to 0.12 μg/ml reported for moxifloxacin (225). *In vivo* efficacy was demonstrated in murine infection models, as both quinolones were found to equivalent to isoniazid (INH) after 4 weeks of treatment (225).

Pharmacokinetic analyses of gatifloxacin and moxifloxacin along with several other quinolone comparators after single oral doses of 400 mg in healthy human volunteers showed good plasma exposure, high bioavailability (≥90%), and no serious adverse event during the study period (226). Phase 2 studies showed promising early bactericidal activity in TB patients with monotherapy at 400 mg daily (227). Addition of moxifloxacin or gatifloxacin to standard treatment regimens in phase 2b studies significantly improved culture conversion after 8 weeks of treatment (228). These *in vitro* and *in vivo* data suggest the possibility of shortening the duration of treatment of tuberculosis by several weeks by including either gatifloxacin or moxifloxacin in the combination drug therapy. Thus far, these quinolones have been safe and well tolerated at a 400-mg daily dosage over extended treatment durations. Phase 3 studies are ongoing and will further evaluate safety and efficacy (http://www.clinicaltrials.gov).

Delamanid. Also in phase 3 clinical development is delamanid (OPC-67683; Otsuka Pharmaceutical Co.) (Fig. 7, compound 4), a nitro-dihydro-imidazooxazole derivative that inhibits mycolic acid synthesis and has shown *in vitro* and *in vivo* activity against *M. tuberculosis* MDR strains (229, 230). This compound displayed an exceptionally low MIC range of 0.006 to 0.024 μg/ml and was also highly active against intracellular *M. tuberculosis* bacilli (230). In a recent phase 2 trial to evaluate safety and efficacy in the treatment of MDR *M. tuberculosis* for 56 days, patients received either 100 or 200 mg delamanid BID in addition to an optimized background regimen (229) (http://www.clinicaltrials.gov). Addition of delamanid was found to be associated with an increase in sputum culture conversion at 2 months among patients with MDR *M. tuberculosis*. Most adverse events were mild to moderate in severity, although QT prolongation was reported significantly more frequently in the groups that received delamanid. These findings suggest that delamanid could enhance treatment options for MDR *M. tuberculosis*.

PA-824. Among the compounds in phase 2 clinical trials for treatment of TB is PA-824, a small-molecule nitroimidazopyran drug candidate (Fig. 7, compound 5) originating from Pathogenesis and under development by the Global Alliance for TB Drug Development. Nitroimidazopyrans inhibit the synthesis of protein and cell wall lipid after activation by a mechanism dependent on *M. tuberculosis* F420 cofactor (231). PA-824 was tested *in vitro* against a broad panel of MDR *M. tuberculosis* isolates and was found to be highly active against all isolates, with MICs of <1 μg/ml (232). The compound was also found to be efficacious in both short-course and long-term mouse infection models. In a recent early bactericidal activity phase 2 study, a PA-824–moxifloxacin–pyrazinamide regimen was found to be potentially suitable for treating drug-sensitive and MDR TB, and the treatments appeared to be safe and well tolerated (233).

SQ109. SQ109 (Fig. 7, compound 6) is an orally active antibiotic for treatment of pulmonary TB under development by Sequella, Inc. (234). It is a 1,2-diamine related to ethambutol and possesses a novel mechanism of action by disrupting cell wall assembly by targeting MmpL3, a transporter of mycobacterial trehalose monomycolate (235). SQ-109 was initially found to have good MICs (~1 μM), 99% inhibition activity against intracellular bacteria, *in vivo* potency, and limited *in vitro* and *in vivo* toxicity (236). The compound received FDA fast track and orphan drug designations in 2007. In the phase 1 clinical trial program, SQ109 was studied at doses of up to 300 mg and exhibited a good safety profile with a >60-h half-life (http://www.sequella.com). It is hoped that SQ109 could become a component in first-line TB drug regimens, potentially simplifying therapy and shortening current TB treatment regimens.

Linezolid. The oxazolidinone antibiotic linezolid (Fig. 3, compound 6) has been found to have efficacy against *M. tuberculosis* and is under investigation in phase 2 clinical trials sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) for use in therapeutic regimens including treatment of patients with extensively drug-resistant (XDR) *M. tuberculosis* (237). Effectiveness at achieving culture conversion among patients with treatment-refractory XDR pulmonary tuberculosis was observed, but numerous patients reported adverse events, including anemia, thrombocytopenia, and/or peripheral and optic neuropathy (238). These results, although promising, suggest a cautious approach for both dosage and length of treatment for linezolid in *M. tuberculosis* infections. These promising microbiological and clinical data have inspired additional research on the oxazolidinone class of antibiotics to find compounds with an improved safety profile.

Sutezolid. One newer oxazolidinone, sutezolid (PNU-40080; Pfizer) (Fig. 3, compound 11), is a sulfur-containing linezolid analog with an active sulfoxide metabolite. The mean MIC was found to be 3.2 times lower than that for linezolid for *M. tuberculosis* clinical isolates with various susceptibilities to isoniazid (INH), rifampin, ethambutol, and streptomycin (239). PNU-100480 also demonstrated improved efficacy in murine models of tuberculosis (240, 241), and earlier sterilization (1 to 2 months) was observed when it was combined with standard TB drugs. In phase 1 clinical studies, doses of up to 600 mg BID were generally safe and reasonably well tolerated for up to 28 days, and no significant safety signals were observed. Sutezolid is currently in phase 2 clinical development and has recently completed a study in newly diagnosed, treatment-sensitive patients with pulmonary TB to assess early bactericidal and whole-blood activities (http://www.clinicaltrials.gov). This study consisted of two experimental arms: one with sutezolid twice daily at 600 mg and the other with sut-

ezolid once daily at 1,200 mg compared with Rifafour (rifampin, 150 mg; isoniazid, 75 mg; pyrazinamide, 400 mg; ethambutol, 275 mg).

Posizolid. Posizolid (AZD5847, AZD2563; AstraZeneca) (Fig. 3, compound 10) (220, 242) was originally in development as a once-daily i.v./oral treatment for staphylococcal infections as an improvement over twice-daily linezolid dosing. However, development was discontinued in 2002 when pharmacokinetics in healthy volunteers did not support once-daily i.v. dosing. The compound was later repositioned for the treatment of tuberculosis by oral administration. Posizolid demonstrated activity against extracellular, intracellular, rapidly dividing, and slowly dividing *M. tuberculosis* in mouse models of tuberculosis, and pharmacokinetics were consistent with once-daily dosing for TB. It was generally safe and well tolerated over 14 days in healthy volunteers (243), although reversible changes in white blood cell (WBC) and reticulocyte counts were observed at the highest exposures tested. AZD5847 is in phase 2 clinical studies to assess the early bacterial activity (EBA) over 14 days at four different doses and schedules (500 mg once daily, 500 mg twice daily, 1200 mg once daily, and 800 mg twice daily) in subjects with newly diagnosed sputum smear-positive pulmonary TB (http://www.clinicaltrials.gov). There is potential for AZD5847 to distinguish itself among TB drugs due to activity against slowly dividing bacteria, activity against intracellular bacilli, and reduced inhibition of human mitochondrial protein synthesis.

SQ609. SQ609 (Sequella, Inc.) (Fig. 7, compound 8), an adamantine-containing hydroxydipiperidine, was identified after screening a 10,240-compound library based on commercially available amino acids and containing a dipiperidine pharmacophore (244). It displayed promising anti-*M. tuberculosis* activity, including against MDR isolates, with a mechanism that targets the mycobacterial cell wall (http://www.sequella.com). SQ609 demonstrated good activity against *M. tuberculosis* strains, inhibiting more than 90% of intracellular bacterial growth at 4 μg/ml without toxicity (244). In addition, *in vivo* efficacy was demonstrated in a mouse infection model, where it completely prevented TB-induced weight loss and improved survival compared to results for mice treated with moxifloxacin or ethambutol. Therapeutic effects continued for 2 weeks after cessation of treatment. Sequella reports that SQ609 has several attributes that support further clinical development, including activity against intracellular *M. tuberculosis*, high specificity for *M. tuberculosis*, good aqueous solubility, oral bioavailability, and a favorable *in vitro* safety pharmacology and ADME profile. It also showed additive or synergistic activity with first-line TB drugs, suggesting that it could added to or replace one of the drugs in the current first-line regimen.

COMPOUNDS FOR THE TREATMENT OF *CLOSTRIDIUM DIFFICILE* INFECTIONS

Over the last decade, there has been a resurgence of *Clostridium difficile* infections causing significant hospital morbidity and mortality in North America and Europe, which surprised most infectious disease experts (245). One strain of *C. difficile*, BI/NAP1/027, has been the cause of most of this increase in infection rates, particularly in North America. Several characteristics of this strain are thought to contribute to its hypervirulence, including increased toxin production, high-level fluoroquinolone resistance (leading to selection over other strains during high fluoroquinolone use), and improved toxin binding (246). The presence of this epidemic strain in North America was first reported in 2005 (247), and an increased infection rate and increased mortality correlating with patient age have also been demonstrated. Before the approval of fidaxomicin in 2012, oral vancomycin was the only agent approved by the FDA for the treatment of *C. difficile* infections although metronidazole is widely used as a first-line treatment. The search for new drugs to treat these infections and prevent recurrence has been an active area for research in recent years.

Surotomycin. Surotomycin (CB-315, CB-183,315; Cubist Pharmaceuticals) (Fig. 8, compound 1), is an investigational lipopeptide oral antibiotic for the treatment of *C. difficile* infections. It is structurally related to daptomycin and appears to share its mechanism of action. When tested against *S. aureus*, surotomycin dissipated the membrane potential of target cells without inducing changes in membrane permeability to small molecules, and it is assumed to do the same against *C. difficile* (248). When assayed against more than 200 *C. difficile* clinical isolates, this antibiotic exceeded the potency of vancomycin by 4-fold and that of metronidazole by greater than 16-fold, and all isolates were inhibited at concentrations of ≤1 μg/ml (249). The drug is bactericidal and stays at the site of infection in the intestinal tract with minimal systemic absorption or disruption of normal bowel flora. In a clinically relevant hamster infection model, it demonstrated potent efficacy in protecting hamsters from lethal *C. difficile* infections during the dosing period, even at low doses of 2 mg/kg, and was similar to vancomycin in rates of disease recurrence in this model (248). In phase 2 trials, surotomycin demonstrated strong cure rates comparable to those for vancomycin and significantly reduced rates of recurrence compared to those with vancomycin (17% compared to 36%, respectively) (http://www.cubist.com). The drug was generally safe and well tolerated. Two phase 3 clinical trials evaluating the safety and efficacy of surotomycin compared with vancomycin are ongoing (http://www.clinicaltrials.gov).

Cadazolid. Cadazolid (ACT-179811; Actelion) (Fig. 8, compound 2) is a quinolonyl-oxazolidinone chimeric antibiotic with structural elements of an oxazolidinone and a quinolone. A phase 2 dose-finding study evaluated the efficacy, safety, and tolerability of three doses of cadazolid (administered orally, twice daily) versus vancomycin (125 mg administered orally, four times daily) for 10 days. The results of this study indicated that the effects of all doses were equivalent or superior to those of vancomycin on key endpoints, including cure rates and sustained cure rates (http://www1.actelion.com). In addition, recurrence rates were lower for all doses of cadazolid than for vancomycin. The drug was safe and well tolerated, with no safety signals identified to date.

LFF571. Researchers at Novartis synthesized and tested 4-aminothiazolyl analogs of the antibiotic natural product GE2270A for activity against *C. difficile* infection. A series of dicarboxylic acid derivatives with solubility and efficacy that were improved by several orders of magnitude compared to those of earlier compounds were discovered, and this led to the selection of LFF571 (Fig. 8, compound 3), a semisynthetic thiopeptide that is an inhibitor of bacterial translation acting via inhibition of elongation factor Tu (250). This compound possesses potent activity against *C. difficile* and most other Gram-positive anaerobes, displaying MIC_{90} values of ≤0.25 μg/ml, with the exception of bifidobacteria and lactobacilli (251). Recently a phase 1 first-in-human clinical trial investigated the safety and pharmacokinetics of single and multiple

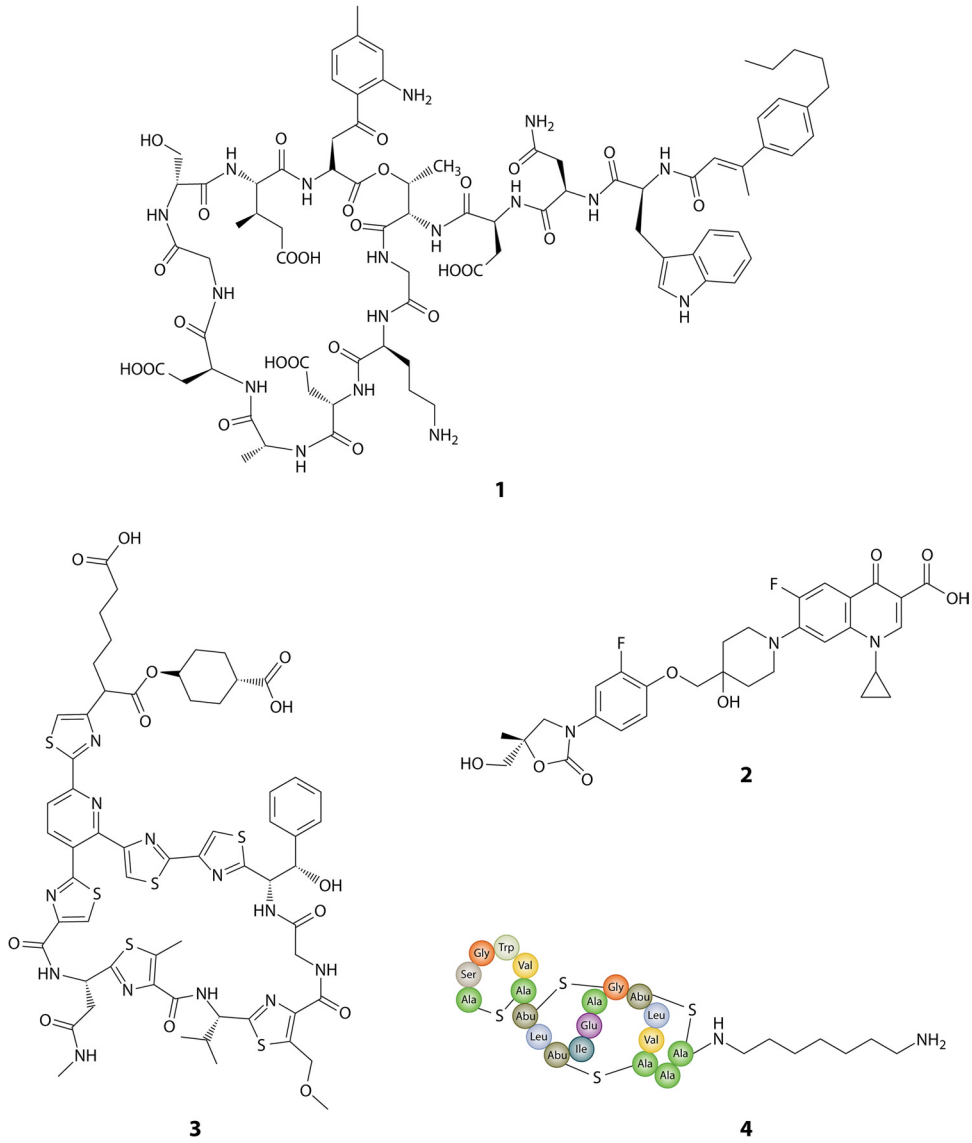

FIG 8 Structures of compounds for the treatment of *C. difficile*. 1, surotomycin; 2, cadazolid; 3, LFF571; 4, NVB302.

ascending oral doses of LFF571 in healthy subjects in a randomized, double-blind, placebo-controlled study (252). The drug was found to be safe and well tolerated and had limited systemic exposure and high steady-state fecal concentrations. A phase 2 clinical trial is currently in progress to assess safety and efficacy of multiple daily dosing of oral LFF571 in patients with moderate *C. difficile* infections (http://www.clinicaltrials.gov).

NVB302. NVB302 (Novacta Biosystems Ltd.) (Fig. 8, compound 4) is a novel type B lantibiotic under evaluation for the treatment of *C. difficile* infections. This compound is not absorbed well, resulting in optimal concentration in the gastrointestinal tract at the site of infection, enhancing efficacy and lessening resistance selection (http://www.novactabio.com). It is highly selective for *C. difficile* versus normal gut flora, which may diminish the chance for recurrent infections. NVB302 displayed noninferiority to vancomycin in the treatment of simulated *C. difficile* infection in an *in vitro* human gut model (253). Novacta recently completed a phase 1 clinical trial in healthy volunteers, and NVB302 was found to be safe and well tolerated, with negligible systemic absorption of the drug and high concentrations recovered in the feces.

CONCLUSIONS

Although antibiotic resistance continues to increase, resulting in exceedingly difficult-to-treat infections caused by multidrug-resistant and panresistant bacteria, antibacterial discovery and development efforts have also been continuing in an effort to confront these pathogens. The loss of resources from the large pharmaceutical companies is a major cause for concern (254), but this has not meant that antibiotic drug development has disappeared (7). In spite of an apparent discovery gap beginning in the 1980s, new classes of antimicrobial agents with novel mechanisms of action are being identified, with many of them appearing over the past 10 to 15 years (Fig. 9). Encouraging information has been presented in this review, showing that the number of investigational antibacterial agents in late-stage development has increased

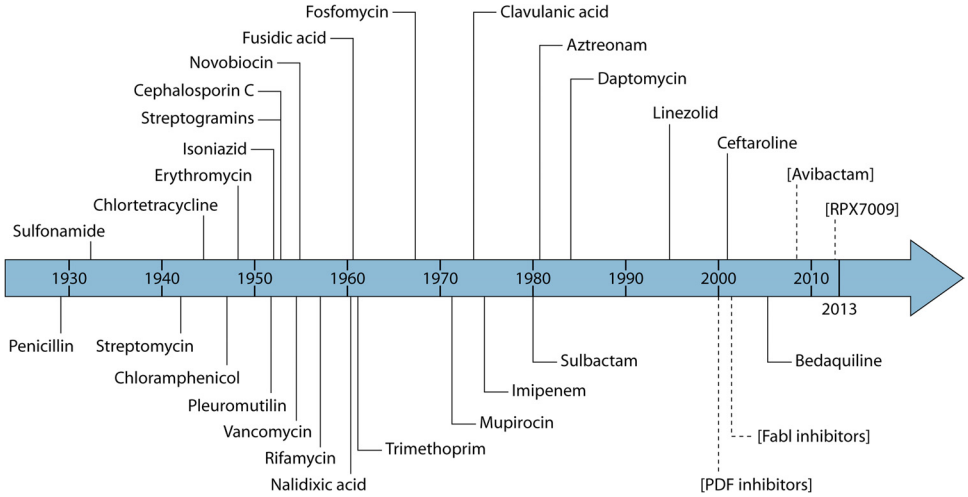

FIG 9 Timeline of the first reports of antibacterial agents or inhibitors with novel structures or activities. Brackets and dashed lines indicate unapproved investigational agents or classes.

considerably since our last overview of the area was presented in 2011 (9). As seen in Fig. 10, a much larger number of antibacterial agents have advanced into phase 3 clinical trials compared to the number in our 2011 survey, suggesting a more robust pipeline than others may have recognized.

Among these investigational agents are many that are effective primarily, or exclusively, against Gram-positive pathogens. Some have argued that there is a limited need for agents active against organisms such as MRSA because of the low resistance rates seen for currently effective agents (254). However, some of the agents described here have distinct advantages over approved agents. These include the glycopeptides oritavancin and dalbavancin, which have the potential to provide single-dose therapy for selected infections. Oxazolidinones with enhanced potency and less toxicity compared to linezolid are in development for treatment of staphylococcal and enterococcal infections, with tedizolid the most advanced in clinical development. DNA topoisomerase inhibitors such as delafloxacin, JNJ-Q2, and ozenoxacin exhibit greater potency than currently available quinolones against MRSA and may provide drugs with reduced resistance propensities that are effective against resistant staphylococci and streptococci. An oral formulation of fusidic acid combined with rifampin may provide another option for the treatment of prosthetic joint infections caused by Gram-positive pathogens. The antistaphylococcal agents with previously unexploited targets include the PDF inhibitor GSK1322322 and the FabI inhibitor AFN-1252, both of which should be watched carefully for the selection of resistance during clinical trials. Because each of these targets a single enzyme, resistance is more likely to emerge than if multiple targets were involved in their mechanisms of action.

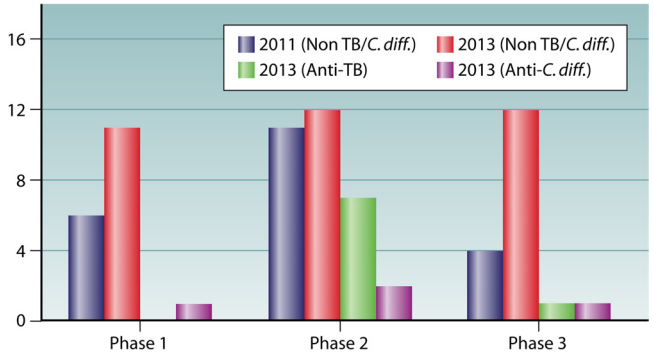

FIG 10 Clinical development status of investigational drugs in the 2011 pipeline (9) compared to 2013. Note that in 2011 agents active against *Clostridium difficile* or *Mycobacterium tuberculosis* were not included in the survey.

Agents in phase 2 and phase 3 clinical trials that have demonstrated antimicrobial efficacy against *M. tuberculosis* are more prevalent than in the past. Perhaps some of the agents most likely to proceed through regulatory filings include moxifloxacin and gatifloxacin, the fluoroquinolones with the greatest potency against mycobacteria, PA-824, delamanid, and a set of oxazolidinones, including linezolid. As with all antituberculosis drugs, these agents will be used in combination therapy to suppress the emergence of resistance. However, the potential for class-related toxicities during long-term use will need to be monitored closely, especially for the fluoroquinolone and oxazolidinones. New agents with the potential to counteract *C. difficile* infections are also on the horizon, including the orally bioavailable drugs surotomycin and cadezolid. Both of these have the potential to provide additional therapeutic options for the treatment of *C. difficile* infections. Some of the most promising new agents are those that may have the ability to treat recalcitrant infections caused by multidrug-resistant Gram-negative pathogens. These infections are most worrisome because there are no approved or efficacious antimicrobial agents available in many nosocomial settings (11, 254). Among the agents that play a role in addressing this issue are plazomicin and eravacycline, protein synthesis inhibitors that have a broad Gram-negative spectrum of activity, including at least some nonfermentative bacteria (10, 55). Perhaps the agents with the greatest potential, however, are the β-lactamase inhibitor combinations in which potent inhibitors of novel structural classes, such as avibactam, MK-7655, and RPX7009, are combined with safe and efficacious β-lactams for the treatment of serious nosocomial infections. These inhibitor combinations are especially effective against bacteria producing many of the serine

β-lactamases, including the widespread KPC carbapenemases that appear in highly resistant *Enterobacteriaceae*. Combination therapy, not only with β-lactamase inhibitors, will be the most likely approach for future anti-infective therapy, especially for infections caused by Gram-negative bacteria.

The industry, however, cannot be complacent. Bacteria will continue to select for resistant strains that can overcome the new agents, and novel agents in new classes will continue to be needed. It is possible, however, that there is at least some hope that we may be able to tackle at least some of our current problems with new agents in the current pipeline.

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We have included references to a number of company webpages describing compounds that are in clinical development, with information current at the time of this review concerning the regulatory status of the agents. Note that the content of these references may be updated on a regular basis and may not be identical to the information cited in the text.

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